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.

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RESEARCH

Summary of adverse drug events for hydroxychloroquine, azithromycin, and chloroquine during the COVID-19 pandemic

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ABSTRACT

Objective: Given the increased use of hydroxychloroquine (HCQ), chloroquine (CQ), and azithromycin (AZM) during the early months of the coronavirus disease 2019 (COVID-19) pandemic, there is a need to evaluate the associated safety concerns. The objective of this study was to summarize the adverse drug events (ADEs) associated with HCQ, CQ, and AZM use during the national COVID-19 emergency and compare the results with known adverse reactions listed in the drugs' package inserts.

Methods: A cross-sectional study design was used. The publicly available Food and Drug Administration Adverse Event Reporting System quarterly data extract files from January 1, 2020 to June 30, 2020 were downloaded. A disproportionality analysis was conducted using the proportional reporting ratio to identify possible ADE signals. A Poisson regression was used to assess if the number of ADE reports for the 3 drugs increased over time.

Results: There was a statistically significant increasing trend in the reported ADEs for both HCQ ($P < 0.001$) and AZM ($P < 0.001$). Before the declaration of the national emergency, there were 592 reported drug-ADE pairs for the 3 drugs compared with 2492 drug-ADE pairs reported after March 13, 2020. These 2492 drug-ADE pairs represented 848 ADEs across the 3 drugs, of which 114 (13.4%) were identified as potential signals including 55 (48.2%) that were not listed in the prescribing information.

Conclusions: Our results showed that the reported ADEs for HCQ and AZM have increased during the COVID-19 pandemic. Differences were observed in both the type of and frequency of the highest reported ADEs for the 3 selected drugs before and after the national emergency declaration. Although causation cannot be determined from ADE reports, further investigation of some reports may be warranted. Our results highlight the need for pharmacovigilance and education of health care professionals on the safety of these drugs when being used for COVID-19 prophylaxis or treatment.

Background

Hydroxychloroquine (HCQ) and chloroquine (CQ) are known treatments for malaria, lupus, and rheumatoid arthritis, but can cause abnormal heart rhythms such as QT interval prolongation and ventricular tachycardia. These risks may increase when these drugs are combined with other drugs known to prolong the QT interval, including the antibiotic azithromycin (AZM), and when patients have other chronic health issues such as heart and kidney disease.[1-3] Given the increased use of these drugs during the coronavirus disease 2019 (COVID-19) pandemic in both an inpatient and outpatient setting, there is a need to evaluate the safety concerns arising from the use of these drugs and explore potential new risks associated with their use in the treatment of a new disease. Despite weak evidence of the efficacy of HCQ and

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Data transparency: The Food and Drug Administration Adverse Event Reporting System quarterly data extract files are publicly available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

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Key Points

Background:

- Prescriptions for hydroxychloroquine, chloroquine, and azithromycin increased in the US during the early months of the pandemic.
- In late March 2020, the U.S. Food and Drug Administration issued an Emergency Use Authorization for the use of oral formulations of hydroxychloroquine and chloroquine in patients hospitalized for the treatment of COVID-19.

Findings:

- There was a statistically significant increasing trend in the reported ADEs for both hydroxychloroquine ($P < 0.001$) and azithromycin ($P < 0.001$).
- Differences were observed in both the type of and frequency of the highest reported ADEs for the 3 selected drugs before and after the national emergency declaration.

CQ in human populations, their promise in in vitro studies led to the incorporation of these drugs in treatment guidelines for COVID-19 early in the pandemic.[4]

In the United States, the President issued a proclamation declaring a national emergency concerning the COVID-19 outbreak on March 13, 2020.[5] Soon thereafter, on March 28, 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of oral formulations of HCQ and CQ in patients weighing 50 kg or more who were hospitalized for the treatment of COVID-19.[6] On April 24, 2020 the FDA, who were aware of reports of serious heart rhythm problems in patients with COVID-19 treated with HCQ or CQ, often in combination with AZM and other QT prolonging drugs, issued a Drug Safety Communication cautioning against the use of HCQ and CQ for the treatment of COVID-19 outside of the hospital setting or as part of a clinical trial because of the risk for heart rhythm problems. In this same communication, the FDA also stated that they were aware of increased outpatient prescriptions for the drugs.[7] Subsequently, on June 15, 2020, the FDA revoked the EUA[6] citing a randomized, double-blind trial that found no statistically significant difference between the drugs and placebo treatments for post-exposure prophylaxis.[8] The revocation also cited research reporting that the drugs lacked a treatment effect.[9]

Two recent studies support the FDA's initial concerns about increased outpatient prescriptions. One study indicated an 80-fold increase in new prescriptions for HCQ and CQ in March 2020, when compared with March 2019, from primary and specialty care physicians who would not normally prescribe these drugs.[10] These data are further corroborated by a study of the the data of prescriptions filled during the pandemic.[11] Both studies point to the use of these drugs outside the original population specified in the EUA. However, these studies do not address if there was a corresponding increase in adverse drug event (ADE) reports. ADEs are injuries resulting from medications and include medication errors, adverse drug reactions, allergic reactions, and overdoses.[12] Investigating the risks associated with these drugs is good pharmacovigilance and of interest to the FDA.[7]

Objective

The objective of this study was to summarize the ADEs associated with HCQ, CQ, and AZM use during the COVID-19 national emergency and compare the results with known adverse reactions listed in the drugs' package inserts.

Methods

A cross-sectional study was conducted. The FDA Adverse Event Reporting System (FAERS) was designed to support the FDA's post-marketing safety surveillance program; the database contains adverse event reports, medication error reports, and product quality complaints that resulted in adverse events that were submitted to FDA.[13] Reports in the database describe ADEs that occurred domestically and internationally. The publicly available FAERS quarterly data extract files from January 1, 2020 to June 30, 2020 were downloaded and a cross-sectional study design was used. The "DEMO," "DRUG," and "REAC" files were used and linked with the primary identifier (PRIMARYID). A deduplication procedure was performed by selecting the highest PRIMARYID for each report. Only the primary suspect drug from a report (ROLE_COD = PS) was included in our analysis. ADE terms were standardized using the Medical Dictionary for Regulatory Activities' preferred terms. Because multiple ADEs can be listed in a report and do not correspond to a specific drug, we included all listed ADEs from a report in our analysis. Reports missing a primary suspect drug or that did not list an ADE were excluded. To ensure we were capturing only new reports during the 6-month period, the date the FDA received the first version of a report (INIT_FDA_DT) had to be on or after January 1, 2020. Both brand and generic names were used to identify the 3 drugs being used for COVID-19 treatment and prophylaxis, namely azithromycin, Zithromax, hydroxychloroquine, Plaquenil, chloroquine, and Aralen. All ADEs and drug names were converted to upper case text for standardization.

Descriptive statistics were calculated using R (version 3.6.3, R Core Team) and Excel (Microsoft Excel for Mac, version 16.40, Microsoft Corporation). A generalized linear model with a Poisson variance function was used to assess if the number of ADE reports for the 3 drugs increased over time, with time in months as the independent variable and the count of ADE reports as the dependent variable. Disproportionality quantifies if the number of ADE reports for a specific drug-ADE pair is higher than expected for spontaneous ADE report data, and disproportionality analyses are commonly used in pharmacovigilance. We conducted a disproportionality analysis using the proportional reporting ratio (PRR). The PRR is calculated by comparing the proportion of a specified ADE for each of the 3 drugs with the proportion of the specified ADE in all other drugs in the data set. The null value for a PRR is 1, meaning that the ADE is reported just as frequently for the drug(s) of interest

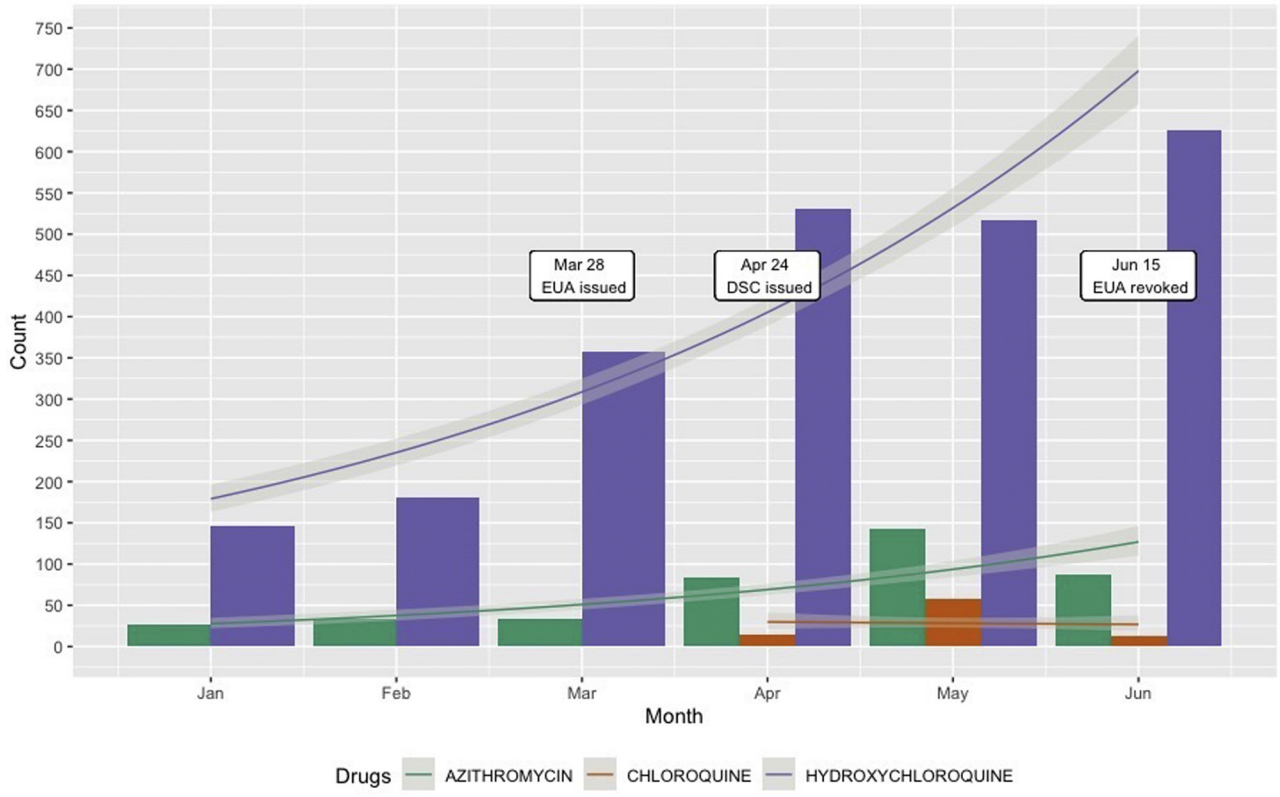

Figure 1. Azithromycin, chloroquine, and hydroxychloroquine adverse events by drug and month, January-June 2020. Abbreviations used: DSC, Drug Safety Communication; EUA, Emergency Use Authorization.

as for all other drugs in the database. Thus, the PRR measures the strength of the association similar to the relative risks (the higher the PRR, the greater the strength of the signal). A possible ADE signal was defined by the accepted thresholds of PRR as greater than or equal to 2, the number of reports for a drug-ADE pair being greater than or equal to 3, and a chi-square of greater than or equal to 4.[14] All drug-ADE pairs entered into the FAERS during the emergency declaration (March 13, 2020 to June 30, 2020) were included in the disproportionality analysis. All data preparation, Poisson regression analysis, and the disproportionality analysis were done using R (version 3.6.3).

Results

After the FAERS quarterly data extract files were cleaned and merged, the data set contained 747,831 ADE reports and 2,119,116 reported drug-ADE pairs that were recorded during the study period. For the 3 drugs of interest, there were 974 ADE reports and 3084 reported drug-ADE pairs. From January 1, 2020 to June 30, 2020, HCQ use accounted for most of the reported ADEs, and the results of the Poisson regression indicated a statistically significant increasing trend in the reported ADEs for both HCQ ($P < 0.001$) and AZM ($P < 0.001$) (Figure 1). There were no ADE reports associated with the use of CQ until April 2020. The first ADE report related to CQ use was recorded on April 2, and the overall trend of CQ ADE reports was constant ($P = 0.797$) throughout the study period. The number of ADE reports was different for the period before and after the declaration of the COVID-19 national emergency. From January 1, 2020 to March 12, 2020, there were 592 reported drug-ADE pairs for HCQ, AZM, and CQ compared with 2492 drug-ADE pairs that have been reported since March 13, 2020. Figure 2 shows the difference in both the type of and frequency of the most frequently reported ADEs for the 3 selected drugs before and after the national emergency declaration. Before the national emergency declaration, the top 3 ADEs were related to maternal exposure during pregnancy (n = 30), drug ineffectiveness (n = 24), and premature delivery (n = 19). Following the national emergency declaration, the top 3 ADEs were related to off-label use (n = 169), hepatitis (n = 102), and prolonged electrocardiogram QT intervals (n = 74).

Table 1 contains the results of the PRR analysis for the period after the national emergency declaration (March 13 to June 30, 2020). Of the 848 reported ADEs, 114 (13.4%) were potential signals. Of those, 59 (51.8%) were listed in the prescribing information, and the remaining 55 (48.2%) were not listed. HCQ had the largest number of potential signals [94 (15.8%)] of which 46 (48.9%) were not listed in the prescribing information. The top 5 potential signals for ADEs not listed in the HCQ prescribing information based on the PRR were COVID-19 treatment, herpes simplex hepatitis, vessel puncture site hemorrhage, clinical trial participant, and a prolonged electrocardiogram QRS complex. The top 5 potential signals for ADEs not listed in the AZM prescribing information based on the PRR were hypertriglyceridemia, premature baby, bradycardia, maternal exposure during pregnancy, and atrial

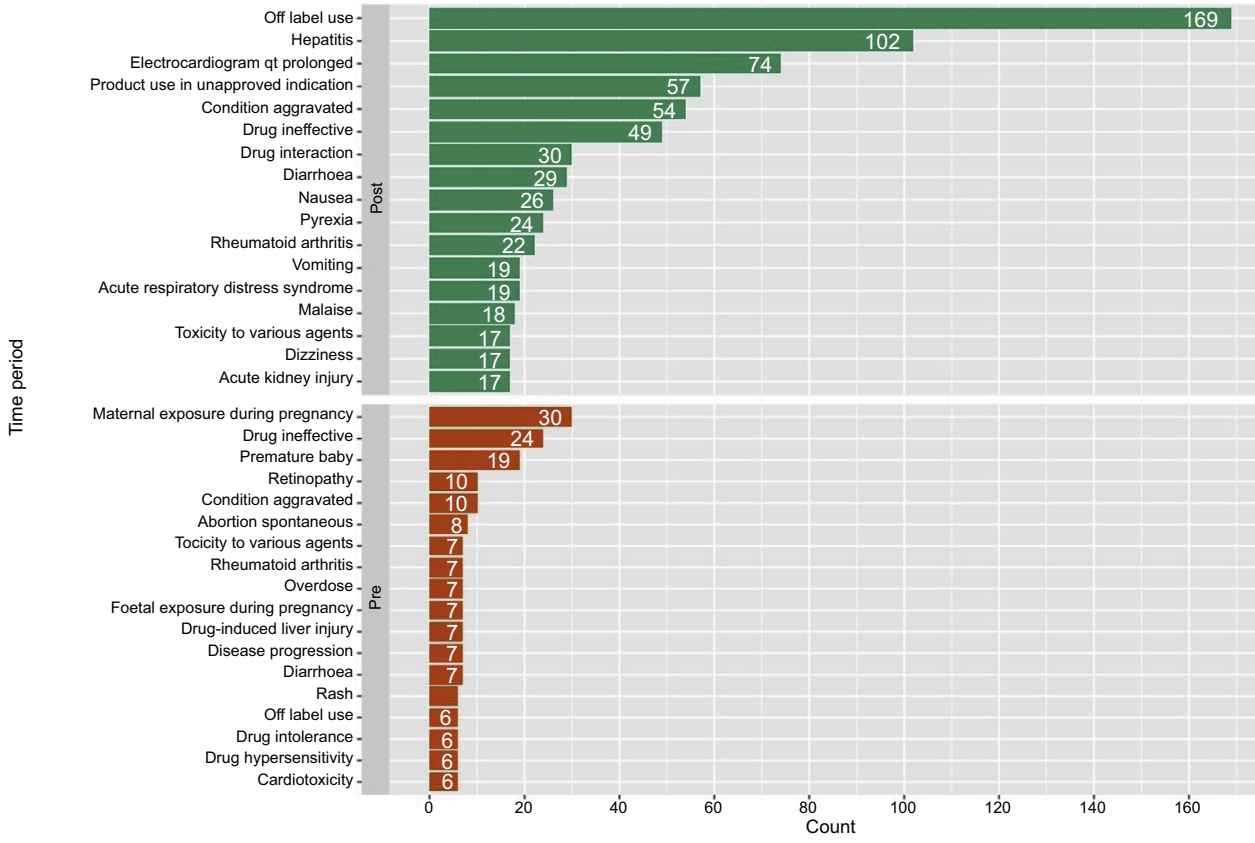

Figure 2. Most frequently reported adverse events for azithromycin, chloroquine, and hydroxychloroquine in FAERS before and after the declaration by the United States of a national emergency related to COVID-19. Abbreviations used: COVID-19, coronavirus disease 2019; FAERS, U.S. Food and Drug Administration Adverse Event Reporting System.

fibrillation. Off-label use was the only potential signal for an ADE not listed in the CQ prescribing information based on the PRR.

Discussion

The results indicate a statistically significant increase in the reported ADEs for both HCQ and AZM that corresponds with the national emergency declaration (Figure 1) and an increase in the prescription of HCQ, CQ, and AZM.[10,11] Although a certain increase in ADEs might be expected given the increased utilization of these drugs, the PRR analysis indicated that half of the ADE signals for HCQ, CQ, and AZM were not listed in the prescribing information and were potentially new signals related to the use of these drugs. Alternatively, they could be previously undescribed symptoms caused by COVID-19 infection. Subsequent clinical review and research are needed to assess causality. In addition to the known ADEs for HCQ, such as higher rates of cardiovascular event reports,[15] we found evidence of ADEs related to herpes simplex hepatitis, vessel puncture site hemorrhage, and a prolonged electrocardiogram QRS complex. Likewise, several ADEs related to the use of AZM were found. These data mirror some of the safety concerns noted by FDA and suggest that their actions were justified. Our study revealed an added concern based on the upward trend in the reported HCQ-related ADEs that continued to the end of June despite the FDA's April 24, 2020 warning and revocation of the EUA on June 15, 2020. Further research should be conducted to evaluate if this trend continued into and beyond July 2020.

Our results suggest that about half of the ADEs might have been prevented because these were known before the use of these drugs for COVID-19. In fact, the FDA's Drug Safety Communication on April 24, 2020 cited that HCQ or CQ can cause QT interval prolongation, increase the risk of QT interval prolongation in patients with renal insufficiency or failure, increase insulin levels and insulin action causing an increased risk of severe hypoglycemia, cause hemolysis in patients with a glucose-6-phosphate dehydrogenase deficiency, and interact with other drugs that cause QT interval prolongation even after discontinuing the drugs because of their long half-lives of approximately 30-60 days.[7]

Of note, after the national emergency declaration there were 41 ADEs referencing COVID-19 in the FAERS data in addition to 169 ADEs reported for "off-label use," 57 for "product use in unapproved indication," and 9 for "clinical trial participant." Although not only for adverse events per se, the reporting gives insight into the drugs' unorthodox indications and the increasing number of ADEs that corresponded with the increased prescription after the national emergency declaration. In addition, the FDA lists the ability to capture "off-label use" as a strength of FAERS.[16] These reports allow the

Table 1
Evaluation of the potential signals occurring after the national emergency declaration, March 13 to June 30, 2020

Drug	No. of ADE reported	No. of potential signals[a] of the reported no. of ADEs, n (%)	Listed ADE or disease related, n (%)	Possible signals for ADEs not listed, n (%)
Azithromycin	184	18 (9.8)	10 (55.6)	8 (44.4)
Chloroquine	68	2 (2.9)	1 (50)	1 (50)
Hydroxychloroquine	596	94 (15.8)	48 (51.1)	46 (48.9)
Totals	848	114 (13.4)	59 (51.8)	55 (48.2)

Abberviation used: ADE, adverse drug event.
[a] A possible signal was defined by the accepted thresholds of PRR $\geq$ 2, number of reports $\geq$ 3, and $\chi^2 \geq 4$.

FDA and researchers the ability to conduct postmarket surveillance of ADEs associated with off-label use. Beyond the fact that HCQ, CQ, and AZM were not effective in treating COVID-19, the associated ADEs contribute to the overall burden of ADEs. Each year, ADEs affect approximately 2 million hospital stays, increase length of stay, and result in 1 million emergency department visits and 125,000 hospital admissions.[12]

There are limitations to the study. First, ADE reports in FAERS are likely underreported.[17] This means that the true number of ADEs associated with the use of these drugs could be higher. Second, ADE reports submitted to FDA do not undergo extensive validation or verification, and, therefore, a causal relationship cannot be established between a product and the reactions listed in a report. Third, ADE reports in the FAERS are subject to issues of data quality and consistency because of a lack of required and standardized fields, missing data, and potential duplicate reports. Despite these limitations, FAERS receives approximately 2 million adverse event reports a year and is used by the FDA and other researchers for postmarket identification and understanding of drug safety issues.[18] Fourth, based on the data in FAERS it is difficult to discern if the drugs were given in an inpatient or outpatient setting. Although the EUA was for inpatient use, current research shows an increase in the utilization of these drugs in outpatient settings.[10,11] The ability to discriminate in FAERS would allow for a more accurate description of the ADEs in the 2 settings. Despite these limitations, this study used the validated PRR measure to detect ADEs associated with the increased use of HCQ, CQ, and AZM during the beginning of the COVID-19 pandemic and contributes to the post hoc understanding of the consequences of their use.

This study focused on the time period from the declaration of the emergency to 2 weeks after the EUA revocation to assess if an increase in ADE reports correlated with an increase in the prescription of these drugs during the early stages of the pandemic. Future research should monitor the prescribing of these drugs beyond this time period and look for additional safety concerns.

Conclusion

Recent studies have shown an increase in prescriptions for HCQ and CQ during the COVID-19 pandemic.[10,11] Given the increased prescribing, the FDA's actions, and the fact that these drugs are being used for a novel virus, a more complete exploration of the consequences of such use is warranted; thus, our goal was to summarize the associated ADEs reported during the COVID-19 national emergency declaration and compare the results with known adverse reactions listed in the drugs' package inserts. Our results show that the reported ADEs for HCQ and AZM have increased throughout the COVID-19 pandemic. Reports of ADEs related to CQ use first appeared after the national emergency declaration in April 2020, and their overall volume has remained low throughout June 2020. Differences were observed in both the type of and frequency of the top 15 reported ADEs for the 3 selected drugs before and after the declaration of the national emergency. Although causation cannot be determined from the ADE reports, further investigation of some reports may be warranted. Overall, our results add further evidence supporting the FDA's decision to revoke the EUA in June 2020 and highlight the need for health care providers to be aware of the possible ADEs when treating COVID-19.

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