PHARMACOTHERAPY

BRIEF REPORT

The Cardiovascular Effects of Treatment with Hydroxychloroquine and Azithromycin

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Hydroxychloroquine combined with azithromycin has been investigated for activity against coronavirus disease 2019 (COVID-19), but concerns about adverse cardiovascular (CV) effects have been raised. This study evaluated claims data to determine if risks for CV events were increased with hydroxychloroquine alone or combined with azithromycin. We identified data from 43,752 enrollees that qualified for analysis. The number of CV events increased by 25 (95% confidence interval [CI]: 8, 42, p=0.005) per 1000 people per year of treatment with hydroxychloroquine alone compared with pretreatment levels and by 201 (95% CI: 145, 256, p<0.001) events per 1000 people per year when individuals took hydroxychloroquine and azithromycin. These rates translate to an additional 0.34 (95% CI: 0.11, 0.58) CV events per 1000 patients placed on a 5-day treatment with hydroxychloroquine monotherapy and 2.75 (95% CI: 1.99, 3.51) per 1000 patients on a 5-day treatment with both hydroxychloroquine and azithromycin. The rate of adverse events increased with age following exposure to hydroxychloroquine alone and combined with azithromycin. For females aged 60 to 79 years prescribed hydroxychloroquine, the rate of adverse CV events was 0.92 per 1000 patients on 5 days of therapy, but it increased to 4.78 per 1000 patients when azithromycin was added. The rate of adverse CV events did not differ significantly from zero for patients 60 years of age or younger. These data suggest that hydroxychloroquine with or without azithromycin is likely safe in individuals under 60 years of age if they do not have additional CV risks. However, the combination of hydroxychloroquine and azithromycin should be used with extreme caution in older patients.

Key Words hydroxychloroquine, azithromycin, coronavirus infections.

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Given the public health significance of coronavirus disease 2019 (COVID-19) and the lack of suitable antiviral agents, hydroxychloroquine alone or in combination with azithromycin has been suggested as a possible therapy.[1] However, there is no evidence from randomized controlled trials that this therapeutic regimen is effective for COVID-19. Observational data showed mixed or conflicting signals,[1–5] making it difficult to determine efficacy. Given the absence of clear therapeutic benefit, many experts have cautioned against the use of these drugs given their potential side effects, especially adverse cardiovascular (CV) reactions.[6,7]

Hydroxychloroquine is a modern form of a drug (quinine) that has been used for hundreds of years to prevent and treat malaria. The first use of quinine is attributed to the Incas,[8] and quinine analogues were first chemically synthesized in 1891.[9] Of hundreds of quinine-related drugs tested during World War II, chloroquine was found to be the most effective for malaria prophylaxis, and, in 1955, hydroxychloroquine was shown to be as effective as chloroquine with fewer side effects.[8]

Quinine and related drugs have immunomodulating effects, and hydroxychloroquine is currently used to treat rheumatoid arthritis and systemic lupus erythematosus.[8] The immunomodulating effects of quinine have been recognized since 1894 when it was used in the treatment of cutaneous lupus.[8]

In addition to hydroxychloroquine, azithromycin has also been proposed as a potential immunomodulating agent.[10] Azithromycin is a macrolide antibiotic that first became available in 1992 to treat respiratory, sexually transmitted, and mycobacterial infections.[11,12]

Some reports suggest that hydroxychloroquine and azithromycin may increase effectiveness against COVID-19 if used together.[1] However, combining hydroxychloroquine and azithromycin may increase CV risks because both have been associated with QT prolongation and severe life-threatening arrhythmias, including torsade de pointes.[6, 13–17] There is also evidence that COVID-19, even without these other medications, may increase CV events.[18] Cardiovascular risks with azithromycin are associated with underlying patient comorbidities.[19] The risk of serious CV events with hydroxychloroquine have generally occurred in patients with underlying CV, renal, or hepatic disorders.[13, 14]

The risk of serious CV events associated with the combination of hydroxychloroquine and azithromycin is currently unknown. Thus, the purpose of this paper is to investigate the CV risks associated with the use of hydroxychloroquine both with and without azithromycin in a large population.

Methods

All enrollees in the Truven Analytics Marketscan Commercial Claims and Encounters and Medicare Supplemental Databases who were exposed to hydroxychloroquine and azithromycin for the years 2001 to 2017 were identified.[20] We included individuals who were newly started on hydroxychloroquine and, at least once while on hydroxychloroquine, also had a dispensing event for azithromycin. We defined newly started as having at least 12 months of prescription drug coverage without dispensing events for hydroxychloroquine. Additionally, in order to determine possible adverse CV events after starting hydroxychloroquine, enrollees had to have an additional 6 months of enrollment, although use of hydroxychloroquine was not required for any minimum duration. We terminated follow-up when the enrollee exited the Truven data, there were more than 3 months without an estimated supply of the medication, or on December 31, 2017 (when our data ends), whichever occurred first.

We calculated the incidence of CV adverse event codes for acute myocardial infarction(AMI; International Classification of Diseases Ninth Revision [*ICD-9*] code 410.x1), stroke (430, 431, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, or 997.02), transient ischemic attack (435.x), unstable angina (411.xx), atrial fibrillation (427.31), atrial flutter (427.32), any CV arrhythmia (427.xx), ventricular arrhythmia (427.1, 427.4, 427.41, or 427.42), or sudden death (798.x) as used in a prior publication looking at adverse events from antibiotic use in administrative data.[19] These codes were converted to ICD-10 using the Centers for Medicare and Medicaid Services (CMS) General Equivalence Mapping Crosswalk.[21] We identified all events where the enrollee had one of these diagnostic codes in either an inpatient or an outpatient claim.

Once the possible adverse events were identified, we assigned each adverse event to occurring during the 12-month lookback period before starting hydroxychloroquine or during follow-up. Events during follow-up were categorized as hydroxychloroquine alone if the enrollee was taking hydroxychloroquine but not azithromycin and hydroxychloroquine and azithromycin if the enrollee was taking both. During follow-up, 100% of enrollee-days by definition included hydroxychloroquine.

Our analysis took the form of a case-crossover study design where each enrollee served as their own control. For each enrollee and exposure status (lookback, hydroxychloroquine alone, and hydroxychloroquine and azithromycin), we computed the incidence rate of the adverse events (number of days with at least one of the adverse event codes/the number of days in that exposure status). We report the additional incidence of these adverse events in the number of events per 1000 people per year of treatment as well as per 1000 people per treatment episode (defined as 5 days of therapy). The 5-day risk was calculated by multiplying the yearly risk by 5 (days) and dividing by 365 (days per year) to present a more interpretable estimate for a short course of treatment. We then compared the rate of the CV adverse events of hydroxychloroquine alone against lookback and hydroxychloroquine and azithromycin against lookback. The absolute change in incidence and 95% confidence interval (CI) were estimated for each comparison using a paired *t* test.

Because infections alone can increase the risk of cardiac complications, we conducted a sensitivity analysis in which we compared the rate of adverse events while people were taking hydroxychloroquine and azithromycin to the rate when people were taking hydroxychloroquine and amoxicillin with or without clavulanate, penicillin, or doxycycline.

Additionally, we stratified by age at start of hydroxychloroquine treatment and sex to explore the potential for age-sex differences in the risk of adverse events. As people with preexisting CV, hepatic, or renal disease are possibly at higher risk, we also report the estimated effects stratified by the presence of hypertension, heart failure, diabetes, hepatic disease, and renal disease. Each of these conditions was defined using the Agency for Healthcare Quality Elixhauser comorbidity definitions.[22] Because hypertension, heart failure, diabetes, hepatic disease, and renal disease are chronic conditions with long latent periods, the patients were categorized as having the comorbidity if they had ever received a diagnosis for it.

Finally, because the primary mechanism through which these adverse events occur is ventricular arrhythmias, we repeated the analysis using only ventricular arrhythmias and sudden death as outcomes.

Results

We identified 43,752 enrollees newly started on hydroxychloroquine treatment and who had at least one dispensing event for azithromycin while taking hydroxychloroquine. The majority of the enrollees were women and over half were aged 40 to 59 years. Full age and sex breakdown are contained in Table 1.

Among enrollees taking hydroxychloroquine, the number of CV events increased by 24.8 (95% CI: 7.5, 42.1, p=0.005) per 1000 people per year of treatment compared with pretreatment levels. During the period when enrollees were taking both hydroxychloroquine and azithromycin, the rate was increased by 200.6 (95% CI: 145.3, 255.9, p<0.001) events per 1000 people per year of treatment. These events translated to an additional 0.34 (95% CI: 0.10, 0.58, p=0.005) CV events per 1000 patients placed on a 5-day treatment regimen of hydroxychloroquine monotherapy and 2.75 (95% CI: 1.99, 3.51, p<0.001) per 1000 patients on a 5-day regimen with both hydroxychloroquine and azithromycin.

The increase in incidence of adverse events in patients taking hydroxychloroquine and azithromycin was not significantly greater than that observed in patients taking hydroxychloroquine and amoxicillin, penicillin, or doxycycline. The rate of complications was nonsignificantly lower in those taking hydroxychloroquine and azithromycin (−94.6 per 1000 person-years, 95% CI: −196, 7.04, p=0.068).

Table 2 demonstrates that these results were driven by the oldest patients. The rate of adverse events increased under both exposure to hydroxychloroquine alone and hydroxychloroquine with azithromycin with increasing age. For women aged 60 to 79 years prescribed hydroxychloroquine, the rate of adverse CV events was

Table 1. Description of Dual Users of Hydroxychloroquine and Azithromycin in Truven Marketscan[20]

Age, yrs	Male (%)	Female (%)
0–17	236 (3.5)	696 (1.9)
18–40	846 (12.4)	7,075 (19.2)
41–60	3010 (44.1)	19,522 (52.9)
61–80	2,434 (35.7)	8845 (24.0)
81+	296 (4.3)	792 (2.1)
Diagnosis[a]		
Lupus	1892 (24.2)	19,512 (41.0)
Rheumatoid arthritis	4227 (54.0)	23,155 (48.7)
Comorbidities		
Hypertension	4240 (62.2)	19,602 (53.1)
Diabetes mellitus	1831 (26.8)	7439 (20.1)
Hepatic disease	686 (10.1)	3330 (9.0)
Heart failure	831 (12.2)	2628 (7.1)
Renal disease	715 (10.5)	2356 (6.4)

[a]Diagnosed within 14 days before first prescription.

67 (95% CI: 23, 113, p=0.003) events per 1000 people per year of treatment (0.92 per 1000 patients on 5 days of therapy), but the rate was 349 (95% CI: 201, 824, p<0.001) when these patients were prescribed both hydroxychloroquine and azithromycin (4.78 per 1000 patients on 5 days of therapy). For patients younger than 60 years, the rate of adverse CV events after treatment with hydroxychloroquine alone or hydroxychloroquine with azithromycin did not differ significantly from zero.

Patients with a history of hypertension or heart failure had significantly greater increases in the risk of adverse outcomes when on hydroxychloroquine monotherapy or both hydroxychloroquine and azithromycin (Table 3). Compared with the overall sample, the increase in incidence of adverse events is nearly 10 times greater on hydroxychloroquine alone and 6 times greater on hydroxychloroquine and azithromycin in those with heart failure. Renal disease had a similar increase in the rate of adverse events increasing by nearly 10-fold on hydroxychloroquine alone and by 4.5 times when on hydroxychloroquine and azithromycin compared with the overall sample. The increases for those with hypertension, hepatic disease, or diabetes were similar to the overall sample. The risk seemed to be lower with azithromycin and hydroxychloroquine compared with other antibiotics, although this finding was only significant for those with diabetes (Table 3).

Repeating the primary analysis but restricting the outcome to only ventricular arrhythmias and sudden death yields similar but nonsignificant results. Ventricular arrhythmias and sudden death increased nonsignificantly when on hydroxychloroquine versus lookback (1.2 additional events per 1000 people per year of treatment, 95% CI: −1.2, 3.5, p=0.335) and when on

Table 2. Increase in Incidence of Cardiovascular Adverse Events[a,b]

Hydroxychloroquine vs lookback per 1000 person years					
Years	0–17	18–39	40–59	60–79	80+
Female	−66 (−207, 74) [0.354]	3 (−38, 45) [0.875]	−10 (−28, 7) [0.249]	67 (23, 113) [0.003]	357 (88, 626) [0.009]
Male	−67 (−159, 26) [0.157]	−22.6 (−94.3, 49.1) [0.537]	−0.5 (−53, 54) [0.986]	75 (−34, 185) [0.179]	489 (−164, 1141) [0.142]
Hydroxychloroquine and azithromycin vs lookback per 1000 person years					
Female	−34 (−190, 123) [0.671]	106 (3, 209) [0.044]	42 (−10, 95) [0.115]	349 (201, 497) [< 0.001]	810 (25, 1595) [0.043]
Male	59 (−166, 285) [0.605]	244 (−214, 703) [0.296]	143 (−48, 335) [0.142]	824 (372, 1277) [< 0.001]	1506 (−76, 3088) [0.062]
Hydroxychloroquine and azithromycin vs hydroxychloroquine and other antibiotic per 1000 person years					
Female	−140 (−390, 109) [0.269]	−66 (−222, 91) [0.409]	9 (−67, 86) [0.811]	−140 (−396, 116) [0.284]	1473 (−255, 3202) [0.095]
Male	−404 (−1403, 595) [0.422]	−87 (−313, 140) [0.453]	−50 (−384, 283) [0.767]	−1290 (−2329, −252) [0.015]	710 (−1608, 3028) [0.545]

[a]Increased incidence rate and 95% confidence intervals.
[b]p values listed in brackets.

Table 3. Increase in Incidence of Cardiovascular Adverse Events[a,b]

	Hydroxychloroquine vs lookback	Hydroxychloroquine and azithromycin vs lookback	Hydroxychloroquine and azithromycin vs hydroxychloroquine and other antibiotic
Hypertension (n=23,832)	40 (12, 68) [0.005]	312 (221, 404) [< 0.001]	−137 (−295, 20) [0.088]
Diabetes mellitus (n=9270)	32 (−16, 79) [0.189]	339 (184, 494) [< 0.001]	−352 (−87, −617) [0.009]
Hepatic disease (n=4016)	18 (−40, 77) [0.536]	292 (80, 503) [0.007]	−348 (−711, 14) [0.060]
Heart failure (n=3459)	334 (206, 464) [< 0.001]	1217 (776, 1657) [< 0.001]	−466 (−1169, 238) [0.195]
Renal disease (n=3072)	214 (110, 318) [< 0.001]	857 (454, 1260) [< 0.001]	−151 (−761, 459) [0.627]

[a]Increased incidence rate and 95% confidence intervals per 1000 person years.
[b]p values listed in brackets.

both hydroxychloroquine and azithromycin versus lookback (5.1 addition events per 1000 people per year of treatment, 95% CI: −5.6, 15.9, p=0.347; data not shown).

Discussion

Our analysis determined that hydroxychloroquine was associated with an increased risk for adverse CV events among patients older than 60 years of age. If patients over 60 years of age are concurrently prescribed azithromycin, the associated CV risk was further increased as much as 5-fold for women aged 60 to 79 years. However, the absolute risk was small. For a 5-day course of therapy, the number needed to harm (NNH) for a single person to have an adverse CV event was 363 for the entire study population (where NNH = 1/rate on hydroxychloroquine plus azithromycin − rate at baseline). For the highest risk group, men over the age of 80 years, the NNH was 69. The risk was also significantly greater for patients with a history of heart failure or renal disease.

The proposed mechanism for increased CV events with these drugs is life-threatening arrhythmias including torsade de pointes.[6] An observational analysis of 90 patients with COVID-19 who received hydroxychloroquine alone or with azithromycin was recently published.[5] These authors found significant QT prolongation with hydroxychloroquine that was even greater with azithromycin and there was one case of torsades de pointes.[5] We found that the overall CV risk was higher in older women which is consistent with some findings that torsades de pointes is more common in women.[6] However, we found the risk for ventricular arrhythmias or sudden death to be lower than when compared with all of the coded CV events. Our findings seem counterintuitive and may be explained by inaccuracies in the coding process of claims data. Therefore, the overall CV risk in our study is likely to be more accurate than specific CV symptoms or events. We found that azithromycin seemed to cause lower risk than other antibiotics when combined with hydroxychloroquine, but this was only significant in those with diabetes. These findings will need to be investigated in prospective studies, especially in subjects with COVID-19.

Bauman and Tisdale reviewed hydroxychloroquine in the era of COVID-19 and cautioned that the half-life of the drug is 1 to 2 months potentially increasing risk for prolonged periods.[6] The half-life of azithromycin is ~68 hours, so this drug could also have effects for long periods of time. We calculated the increased risk with 5-day courses of hydroxychloroquine alone or with azithromycin to simulate a short course of therapy that might be used for COVID-19. Risks could continue after the regimen is stopped due to the prolonged duration of effect, especially in elderly patients. Additionally, some studies testing prophylaxis or treatment regimens with hydroxychloroquine are using the drug for up to 30 days, which would also lead to potentially higher risk than our 5-day estimates.[1–5]

These results are subject to some limitations. People at high risk for CV adverse events may not be treated with azithromycin or hydroxychloroquine. In addition, all enrollees were taking hydroxychloroquine long term, most likely to manage lupus or rheumatoid arthritis. Patients with rheumatoid arthritis and lupus are at a higher risk for CV disease. Thus, our sample may not be representative of patients with COVID-19. Second, we calculated the 5-day incidence to provide a more valid estimate for a short course of therapy. However, this calculation assumes that risk is the same early in the course of treatment (first 5 days) as later in a year-long course of treatment. It is likely that risk in vulnerable populations, including those with COVID-19, may actually be higher during an acute infectious event. Third, outcomes were based on billing codes submitted as insurance claims. The findings are limited by the accuracy of the billing codes used to define the clinical diagnosis. Additionally, sudden death would only be captured if it occurred in a health care setting and coded on the billing form. Deaths that occurred outside of the clinic or hospital would not be captured in these data. Finally, the risks of hydroxychloroquine increase with length of use.[13, 14, 23] The expected duration of therapy for patients taking both hydroxychloroquine and azithromycin for treatment of COVID-19 is potentially only 5 to 10 days. Thus, the risks may be lower for patients with COVID-19 who would take these drugs for shorter periods of time.

Our results suggest that the use of hydroxychloroquine and azithromycin for patients taking them for lupus or rheumatoid arthritis, is likely safe for patients under 60 years of age. This conclusion may not be true for patients with COVID-19 where there may be additional CV effects. For older patients and those at high risk

of CV events, the risk needs to be considered against the potential benefit of treating COVID-19. Other authors have suggested that QT intervals should be measured at baseline and during therapy and hypokalemia, hypomagnesemia, and hypocalcemia should be corrected.[6] These suggestions seem prudent but our findings suggest that there may be other CV risks besides QT prolongation with hydroxychloroquine. Because these patients did not receive these drugs for COVID-19, additional research is needed to determine whether risk of CV events is increased during COVID-19 treatment.

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