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Conflicts of interest

None disclosed.

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Chronic hydroxychloroquine therapy and COVID-19 outcomes: A retrospective case-control analysis

To the Editor: Hydroxychloroquine (HCQ) has failed to show significant therapeutic benefit for patients with coronavirus disease-2019 (COVID-19) in recent studies, although interest in this medication's potential pre- and postprophylactic efficacy remains, with 1 retrospective study showing reduced COVID-19 infection among patients taking chronic HCQ.[1,2] In this study, we sought to evaluate COVID-19 clinical outcomes in patients taking chronic HCQ for an underlying condition as well as in a matched cohort not taking HCQ at time of COVID-19 diagnosis.

Table I. Hydroxychloroquine indication, dosage, and duration at time of COVID-19 diagnosis

HCQ indication, dosage, and duration (N = 50)	n (%)
HCQ indication	
Systemic lupus erythematosus	17 (34.0)
Rheumatoid arthritis	11 (22.0)
Connective tissue disease overlap syndromes	9 (18.0)
Sjögren syndrome	6 (12.0)
Mixed connective tissue disease	2 (4.0)
Undifferentiated connective tissue disease	1 (2.0)
Erythema nodosum during pregnancy	1 (2.0)
Carcinoid	1 (2.0)
Myalgic encephalomyelitis/ chronic fatigue syndrome	1 (2.0)
Acquired hypogammaglobulinemia	1 (2.0)
HCQ dosage	
200 mg HCQ daily	13 (36.0)
200 mg HCQ 2 times daily (400 mg total)	36 (72.0)
200 mg HCQ 3 times daily (600 mg total)	1 (2.0)
Mean duration of HCQ therapy before COVID-19 diagnosis (IQR)	28 (14.25-44.25) months

COVID-19, Coronavirus disease-2019; *HCQ*, hydroxychloroquine; *IQR*, interquartile range.

We identified all patients with severe acute respiratory syndrome coronavirus 2 seen at New York University from March to April 2020 using *International Classification of Diseases, 10th revision* codes and included patients taking HCQ for ≥6 weeks before their COVID-19 diagnosis. Control subjects were randomly selected from the remaining severe acute respiratory syndrome coronavirus 2−positive patients with automated matching for age, gender, and immunosuppressive medication using SPSS software (SPSS Inc, Chicago, IL). Baseline clinical characteristics and outcomes were compared using Pearson χ^2, independent sample *t* test, and Mann−Whitney tests using 2-tailed significance (significance set as $P < .05$).

We identified 50 patients taking chronic HCQ for ≥6 weeks before their COVID-19 diagnosis and 103 matched control subjects who were not taking HCQ at the time of their COVID-19 diagnosis (Table I). There was no significant difference in age, sex, overall use of iatrogenic immunosuppressive medications, or COVID-19 risk factors between the groups (Table II). However, in the control group, there was a significantly higher rate of organ transplantation (2.0% vs 26.2%, $P < .001$), and consequently a higher rate of chronic tacrolimus

Table II. Demographics and clinical outcomes of the study population

	Pre-exposure HCQ (N = 50)	Matched no pre-exposure HCQ (N = 103)	P value
Mean age, y (±SD)	47.2 ± 2.4	49.8 ± 1.4	.282
Sex, n (%)			
Male	8 (16.0)	24 (23.3)	.197
Female	42 (84.0)	79 (76.7)	
Race, n (%)			
White	29 (58.0)	49 (47.6)	.624
Black	15 (30.0)	24 (23.3)	
Asian	2 (4.0)	7 (6.8)	
Other (Pacific Islander, Native American)	0 (0.0)	0 (0.0)	
Unknown	4 (8.0)	14 (13.6)	
Ethnicity, n (%)			
Hispanic	14 (28.0)	25 (24.3)	.959
Non-Hispanic	36 (72.0)	64 (62.1)	
Taking immunosuppressant	28 (56.0)	55 (53.4)	.762
Comorbidities, n (%)			
Mean BMI, kg/m^2 (±SEM)	31.7 ± 1.2	30.5 ± 0.7	.347
Cancer	2 (4.0)	3 (2.9)	.972
Hypertension	21 (42.0)	44 (42.7)	.933
Coronary artery disease	4 (8.0)	7 (6.8)	.787
Congestive heart failure	0 (0.0)	6 (5.8)	.082
Asthma	9 (16.0)	13 (12.6)	.454
Chronic obstructive pulmonary disease	1 (2.0)	3 (2.9)	.740
Obstructive sleep apnea	5 (10.0)	10 (9.7)	.955
Chronic kidney disease	5 (9.8)	12 (11.7)	.761
End-stage renal disease	4 (8.0)	16 (15.5)	.195
Diabetes mellitus	7 (14.0)	28 (27.2)	.053
Organ transplant	1 (2.0)	27 (26.2)	<.001
HIV	0 (0.0)	2 (1.9)	.321
Autoimmune disease	47 (94.0)	30 (28.3)	<.001
Pregnant	3 (6.0)	4 (3.9)	.584
Mean no. of days of COVID-19 symptoms before diagnosis (IQR)	4 (2-8)	4 (2-7)	.932
Level of care, n (%)			
Not hospitalized/ambulatory	29 (58.0)	52 (49.1)	.468
Hospitalized	17 (34.0)	45 (42.5)	
ICU	4 (8.0)	9 (8.5)	
Mean no. of days of duration of stay (IQR)			
Full hospitalization	5.0 (3.0-11.0)	8.5 (5.8-18.0)	.123
ICU stay	9.0 (6.5-24.5)	17.0 (7.5-26.5)	.825
COVID-19 treatment, n (%)			
Glucocorticoids	2 (4.0)	3 (2.9)	.723
Chloroquine	0 (0.0)	0 (0.0)	—
Hydroxychloroquine	50 (100.0)	60 (58.3)	<.001
Azithromycin	28 (54.0)	55 (53.4)	.855
Lopinavir/ritonavir	6 (12.0)	2 (1.9)	.009
Remdesivir	0 (0.0)	1 (1.0)	.485
Interleukin-6 inhibitor	1 (2.0)	15 (14.6)	.017
Convalescent plasma	0 (0.0)	2 (1.9)	.321
Ceftriaxone*	6 (12.0)	16 (15.5)	.559
Complications among hospitalized patients, n (%)	n = 21	n = 54	
Invasive mechanical ventilation	4/21 (19.0)	10/54 (18.5)	.958
Hemodialysis	0/21 (0.0)	7/54 (13.0)	.083
ECMO	0/21 (0.0)	1/54 (1.9)	.530
Venous thromboembolism	1/21 (4.8)	6/54 (11.1)	.396
Disseminated intravascular coagulation	0/21 (0.0)	0/54 (0.0)	—

Table II. Cont'd

	Pre-exposure HCQ (N = 50)	Matched no pre-exposure HCQ (N = 103)	P value
Disposition, n (%)			
Discharged	16/21 (76.2)	43/54 (79.6)	.250
Death	4/21 (19.0)	11/54 (20.4)	.601

BMI, Body mass index; *COVID-19*, coronavirus disease-2019; *ECMO*, extracorporeal membrane oxygenation; *HCQ*, hydroxychloroquine; *ICU*, intensive care unit; *IQR*, interquartile range; *SD*, standard deviation; *SEM*, standard error of the mean.

*Empiric use for bacterial pneumonia prophylaxis or treatment.

and mycophenolate use in this group (Supplemental Table I available via Mendeley at https://data.mendeley.com/datasets/6gmpg43rvm/1); subgroup analysis excluding patients taking tacrolimus or mycophenolate was performed. COVID-19 therapies were statistically similar other than lopinavir/ritonavir (more frequent in the chronic HCQ group) and interleukin-6 inhibitors (more common in the control group; Table II). All patients on chronic HCQ continued to take HCQ upon COVID-19 diagnosis, and 60 control subjects (58.3%) were treated with HCQ for COVID-19.

Clinical outcomes between groups did not differ on any parameter (Table II). Specifically, level of care (34.0% vs 42.5% requiring hospital admission; 8.0% vs 8.5% intensive care unit admission, $P = .468$), length of hospital stay (5.0 vs 8.5 days, $P = .123$), length of stay in the intensive care unit (9.0 vs 17.0 days, $P = .825$), hospital complications (intubation for example: 19% vs 18.5%, $P = .958$), and mortality (19% vs 20.4%, $P = .250$) did not differ (Table II). Three separate subgroup analyses were performed: excluding all those 1) undergoing chronic immunosuppressive therapy, 2) taking chronic tacrolimus or mycophenolate, and 3) taking lopinavir/ritonavir or anti—interleukin-6 treatment. Outcomes did not differ across any outcome upon subgroup analysis.

This retrospective case-control study from a large hospital system at the epicenter of the COVID-19 pandemic found that chronic HCQ was not associated with improved clinical outcomes of COVID-19. Thus, similar to studies showing no treatment or postexposure benefit to HCQ,[1,3] this study suggests no pre-exposure prophylactic benefit, particularly among those with autoimmune disease. Moreover, while patients with autoimmune disease may have worse viral illness outcomes,[4] our results suggest that those taking chronic HCQ do not experience worse COVID-19 outcomes.

Our study's retrospective design limits its generalizability. In addition, the relatively small cohort size, heterogeneity of groups, and inability to perfectly match groups inherently influences results and reduces power to detect smaller differences in outcomes. Notably, there was a higher rate of organ transplantation in the control group; however, subgroup analysis excluding those taking chronic tacrolimus or mycophenolate did not alter results. Moreover, HCQ was commonly administered for an autoimmune condition rather than as pre-exposure prophylaxis. In addition, several control subjects did receive HCQ therapy for COVID-19, potentially limiting the detection of differences between groups. Finally, dosing of chronic HCQ therapy and HCQ for pre-exposure prophylaxis may differ, although the former is typically higher.[5] Therefore, while our results did not find a benefit to chronic HCQ therapy before COVID-19 infection, larger prospective studies of the general population or select high-risk populations may be warranted to evaluate the efficacy of HCQ dosed specifically as a form of pre-exposure prophylaxis.

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Conflicts of interest

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Effect of dupilumab on allergic contact dermatitis and patch testing

To the Editor: Although the pathogenesis of allergic contact dermatitis (ACD) has been classically thought to be driven predominantly by Th1, its complex pathophysiology is now accepted to include Th2, Th17, and Th22 pathways.[1] Due to the involvement of the Th2 pathway and concomitant ACD diagnosis in many patients with atopic dermatitis (AD), numerous reports have recently described the use of dupilumab in patients with ACD.[2] A systematic review was conducted to better understand the effect of dupilumab on ACD and patch testing results.

This systematic review was registered in PROSPERO (CRD42020193449) and followed PRISMA guidelines.[3] We searched Medline and EMBASE databases on June 20, 2020 using the following terms: "dermatitis," "allergic contact dermatitis," "hand dermatitis," "facial dermatitis," "patch testing," AND "dupilumab" (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/b74xk7fzgy.1). The search yielded 1099 studies, of which 1024 were excluded after title/abstract screening and 56 were excluded after full-text screening for the following reasons: no history of ACD prior to dupilumab (n = 42), study not evaluating the effect of dupilumab on ACD/patch testing (n = 7), nonprimary research article (n = 4), or non-English article (n = 3). Original studies that reported at least 1 patient with ACD on dupilumab treatment were included.

From 19 studies, 72 patients (mean age, 54.34 years) with prior history of ACD were included (Table I). Of the 72 patients, 44 reported on the clinical effects of dupilumab on ACD, 25 on the effects of dupilumab on patch testing, and 3 on both. Of the 47 patients with clinical results, dupilumab resulted in clearance of ACD for 9 patients, partial improvement for 31, no improvement for 4, and worsening for 3. Of the 9 patients who achieved clearance, 6 had miscellaneous personal care products and 2 had fragrances as the main clinically relevant allergens on patch testing. Notably, of the 18 patients with hand involvement, 17 improved with dupilumab use.

Between the 28 patients with additional post dupilumab patch testing results, the same allergen was tested prior to, and while on, dupilumab in 144 occasions. Of the 144 pairs, 17 were lost and 8 were newly positive, while 71 were persistent (48 unknown; Table II). Dupilumab-induced inhibition of the Th2 pathway resulting in Th1, Th17, or Th22 polarization may explain the inconsistent patch testing results.[4] Therefore, depending on the response pathway, certain responses may be lost, unaffected, or worsened. For example, through patch testing and subsequent genomic data analysis from biopsies, Dhingra et al[1] found that nickel had high Th1/Th17 polarization and that fragrance demonstrated strong Th2/Th22 polarization. In alignment with these findings, fragrance and balsam of Peru were 2 allergens that lost positivity post dupilumab initiation (Study 3; Table II). Moreover, fragrance and/or balsam of Peru were also clinically relevant allergens in 2 patients who achieved clearance and 7 patients with improvement on dupilumab (Study 4, 5, 8, and 18; Table I).

It is important to note that the primary management is to identify allergens and then remove them, especially keeping in mind the cost of dupilumab at this time. However, this review demonstrates the potential for dupilumab use in patients with recalcitrant ACD. Responses to dupilumab may also vary, depending on the allergen, which was noted with fragrance and balsam of Peru in our study. Limitations of this review include reliance on case reports and series, a small number of patients and patch testing results, nonstandardized data, and overlapping concomitant skin conditions, which may have limited the ability to evaluate the isolated effects of dupilumab on ACD. Moreover, quality assessment using an established tool for case reports/series showed that the majority of the studies did not discuss alternative causes that may explain the results.[5] Larger standardized trials are needed to better understand the effects of dupilumab on ACD and patch testing results and to delineate whether certain patients may be better suited for treatment based on potential patterns of allergen-specific responses to dupilumab.