Hydroxychloroquine ineffective for COVID-19 prophylaxis in lupus and rheumatoid arthritis

The viewpoint of Graef *et al* resonates more each day.[1] In a pandemic where the cries for certainty were met with a flow of mixed early study results, they admonish *festina lente ('make haste slowly')*! Since Graef, there have been many studies of hydroxychloroquine (HCQ) for treating COVID-19. These include a randomised controlled trial of 150 mild-to-moderate patients and three large observational studies, all inpatient studies that failed to show benefit of HCQ treatment for COVID-19.[2–5] Now a new inpatient study, with >80% administered HCQ within 24 hours, finds HCQ associated with substantial mortality reduction.[6] *Festina lente* indeed! A look at HCQ as prophylaxis, where its long half-life can be leveraged, may help.[7]

Bozzalla Cassione and colleagues described a northern Italian cohort of 165 patients with systemic lupus erythematosus (SLE).[8] HCQ users had 50% greater risk of COVID-19 (7.9% vs 5.3%; 95% CI for the difference −9.9% to 9.7%), but were limited by just 12 patients with COVID-19 and possible bias due to concomitant immunosuppressive therapy. A Belgian study of 225 patients with SLE found 7.9% of HCQ users and 8.2% of non-HCQ users had COVID-19 (95% CI for the difference −6.7% to 9.5%), and another Italian study of 914 rheumatologic patients found no preventive benefit for HCQ (0.89% vs 0.62%; 95% CI for the difference −0.84% to 4.28%).[9 10] These studies also had few cases (18 and 6) and possible confounding of immunosuppressive therapy. These three studies convincingly prove that HCQ users get COVID-19. However, they all lacked the sample size for meaningful CIs and could not rule out a strong preventive effect for HCQ. We employed a different methodology that accesses a larger population and expands the cohort to include both patients with SLE and rheumatoid arthritis (RA). This substantially increased the sample size despite only including patients on immunosuppressive therapy to minimise patient heterogeneity in sequestering behaviour and prioritisation for virus testing. If HCQ is effective prophylaxis, then the proportion of patients with SLE/RA on immunosuppressants using HCQ should be less for COVID-19 cases than for the general population.

We queried the commonly used TriNetX Research Network, a federated health research network that aggregates electronic health records from 36 US healthcare organisations (HCOs). Queries return population counts ≥10 patients. We included patients ≥18 years old with SLE or RA and a prescription for an immunosuppressant, diagnosed with COVID-19 since 20 January 2020. An outpatient encounter during the prior year was required to increase sensitivity of diagnoses and prescriptions. We then determined the proportion prescribed HCQ in the prior year. SLE/RA diagnoses and prescriptions were within the year preceding index diagnosis. With 90-day prescriptions and three refills common, many patients get one prescription per year, so only one prescription was required for HCQ or immunosuppressants.

We considered two control groups for the year prior to the COVID-19 study period[1]: patients diagnosed with influenza/pneumonia/other lower respiratory infection (I/P/LRI), as a group with similar symptoms, and[2] everyone with an outpatient visit (OP). Diagnoses were based on ICD-10 codes and prescriptions were identified using the Veterans Affairs Drug Classification System. Data were accessed on 13 July 2020.

A total of 159 patients with COVID-19 met criteria, 22.0% SLE and 80.5% RA (four diagnosed with both) (table 1). Also, 18.9% were hospitalised on day of diagnosis. This compared with 2609 I/P/LRI (22.5% hospitalised) and 32 599 OP. The proportion taking HCQ was similar for COVID-19 and I/P/LRI (34.6% vs 31.4%; CI for difference −4.4% to 10.8%; Fisher's exact test p=0.4290) and OP (34.6% vs 32.7%; CI for difference −5.5% to 9.4%; Fisher's exact test p=0.6115). Hypothesis that HCQ provides 25% protection was rejected versus I/P/LRI (p=0.0098) and OP (p=0.0252). To check if HCQ users only used HCQ for treating COVID-19 symptoms prior to diagnosis, we reran the analysis excluding HCQ prescriptions ≤14 days before COVID-19 diagnosis. This eliminated two HCQ users, as expected for refills in a 14-day period. We reran the analysis for patients under 65. Proportions using HCQ were even more similar: 37.2%, 37.0% and 36.9% for COVID-19, I/P/LRI and OP, respectively.

HCQ was not associated with COVID-19 prevention. A strength of this study is all patients were on an immunosuppressant, with similar high-risk status for COVID-19 regardless of HCQ use. A limitation is that a few patients might be misclassified as non-HCQ users if they had an immunosuppressant prescription in the HCO but filled their HCQ prescription(s) outside that HCO. While we only had data for prescriptions written, prescriptions filled and medications taken reflect real world adherence.

Our results suggest HCQ lacks *in vivo* activity against SARS-CoV-2, which might help explain seemingly contradictory treatment studies. Without antiviral activity, the success or failure of HCQ in treatment is likely due to immunomodulation, anti-inflammatory and anti-thrombotic effects, which may be

Table 1 Proportion of patients taking hydroxychloroquine: COVID-19 vs two control groups

	COVID-19	Influenza/ pneumonia/LRI	CI for difference (COVID-19 vs I/P/LRI)	Any outpatient visit	CI for difference (COVID-19 vs OP)
Age 18 and over					
No of patients, N	16 869	198 114		3 970 695	
Lupus or RA on an immunosuppressant, N	159	2609		32 599	
Hydroxychloroquine, % (N)	34.6% (55)	31.4% (819)	(−4.4% to 10.8%) p=0.4290	32.7% (10 645)	(−5.5% to 9.4%) p=0.6115
Age 18–64					
No of patients, N	13 327	128 280		2 715 365	
Lupus or RA on an immunosuppressant, N	121	1477		20 256	
Hydroxychloroquine, % (N)	37.2% (45)	37.0% (547)	(−8.8% to 9.1%) p=1.0000	36.9% (7473)	(−8.3% to 8.9%) p=1.0000

I/P/LRI, influenza/pneumonia/other lower respiratory infection; LRI, lower respiratory infection; OP, outpatient; RA, rheumatoid arthritis.

more beneficial earlier. Further, more severely ill patients may be especially vulnerable to HCQ's cardiotoxicity. Or maybe it's too soon to make conclusions. *Festina lente!*

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