

Predictors of Unsuccessful Hydroxychloroquine Tapering and Discontinuation: Can We Personalize Decision-Making in Systemic Lupus Erythematosus Treatment?

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Objective. Hydroxychloroquine (HCQ) is a key systemic lupus erythematosus (SLE) drug, making concerns of drug shortages grave. Our objective was to evaluate factors associated with poor outcomes after HCQ taper or discontinuation in SLE.

Methods. We studied 5 Canadian SLE cohorts between 1999 and 2019, following patients from the date of HCQ tapering (cohort 1) or discontinuation (cohort 2). A composite outcome was defined as any of the following: a need for therapy augmentation, an increase (of at least 4 points) in the Systemic Lupus Erythematosus Disease Activity Index 2000 score, or hospitalization for SLE. In each cohort, multivariable Cox regression was used to identify demographic and clinical factors associated with time to the earliest of these events. A third cohort continuing to receive HCQ was also studied, to assess whether the same factors influenced the outcome even when the HCQ dose was unchanged.

Results. The poor outcome rate, per 100 person-years, was 35.7 (95% confidence interval [95% CI] 31.6–40.3) in the HCQ taper cohort (n = 398), 29.0 (95% CI 25.5–33.0) in the discontinuation cohort (n = 395), and 16.1 (95% CI 13.2–19.6) in the maintenance cohort (n = 395). In patients tapering HCQ, baseline prednisone use was independently associated with greater risk of poor outcomes. In the discontinuation cohort, the risk of poor outcomes was greater for Black patients and those diagnosed with SLE at age ≤ 25 years. Among those maintaining HCQ, baseline immunosuppressive use and First Nations ethnicity were associated with poor outcomes.

Conclusion. We identified demographic and clinical factors associated with poor outcomes after HCQ taper/discontinuation. This information is critical in the current setting of potential shortages, but over the long term, such information could inform personalized therapies.

INTRODUCTION

Hydroxychloroquine (HCQ) is a cornerstone medication for systemic lupus erythematosus (SLE) (1), and sustained HCQ use might greatly reduce disease flares (2–4). However, there is

concern over retinal toxicity, an irreversible complication that may affect 20% of patients after long-term exposure (5). Uncertainties about the relative risks/benefits of long-term treatment are a primary concern voiced by patients with SLE (6), and almost one-third of patients with SLE discontinue HCQ treatment by 5–8 years (7).

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SIGNIFICANCE & INNOVATIONS

- Although some patients may do well after reducing therapy, others will have potentially life-threatening complications related to systemic lupus erythematosus (SLE) flares, and there is no information available to guide individual decision-making.
- Three cohorts of patients with SLE who were tapering, stopping, or maintaining hydroxychloroquine (HCQ) were evaluated. The crude flare rate was significantly lower in patients maintaining HCQ therapy than in those tapering or discontinuing the drug.
- Non-White patients (especially Black, Asian, or First Nations patients), those age ≤ 25 years at SLE diagnosis, and those with active disease, including patients receiving prednisone or immunosuppressors, are at higher risk of having flares.
- Our results suggest caution in tapering or discontinuation of HCQ in some groups of patients with SLE. The identification of these predictors is an important approach to promote personalized medicine to avoid unnecessary toxicities, as well as to monitor for flares in situations such as the current setting of potential HCQ shortages due to interest in this drug as a therapy for COVID-19.

On an individual level, patients with SLE and clinicians struggle with many treatment decisions, since there is little information available on tapering or stopping HCQ to guide individual decision-making. Some patients may do well after HCQ withdrawal, but others will have potentially life-threatening complications (8). Recently, new concerns have arisen regarding HCQ shortages for patients with SLE due to potential COVID-19 treatment (9,10). Clearly, we need better predictors of flare risk after HCQ is lowered or discontinued. The aim of this study was to identify baseline factors associated with a poor outcome once HCQ is tapered or discontinued in SLE.

PATIENTS AND METHODS

Data sources. Our study combined data from 5 clinical SLE cohorts in Canada (McGill University Health Centre [MUHC] in Montreal, CHU de Québec–Université Laval in Quebec City, Dalhousie University in Halifax, University of Manitoba in Winnipeg, and the Southern Alberta Registry for Lupus Erythematosus at the University of Calgary). The cohorts enrolled unselected patients age ≥ 18 years who met American College of Rheumatology criteria for SLE (11) at the time that they presented to each center (including both incident and prevalent cases). The enrollment and follow-up period spanned January 1999 to January 2019.

Data on demographic, medication, and clinical variables were collected in a standardized manner at enrollment as well as annually and were submitted to the coordinating center at the MUHC for data harmonization. Ethics approval was

obtained from the institutional review boards at all participating sites.

Study population. We studied adult patients with SLE exposed to HCQ during the study period. Starting from the first visit with HCQ exposure, we identified patients receiving a lower dose or discontinuing HCQ at a follow-up visit. We created 1 cohort to study patients from the time they lowered their HCQ dose: in that case, time zero was the date of the first reduction of HCQ dose. Patients were right censored if they discontinued HCQ completely (for any reason), as they then entered the cohort of patients who had discontinued HCQ (where the date of first HCQ discontinuation was defined as time zero). Patients who discontinued HCQ but started chloroquine right away were not included in the discontinuation cohort, as they were still taking an antimalarial. Patients were followed until the outcome of interest, end of the study period (February 2019), death, or loss to follow-up (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24548>).

HCQ use was assumed to be constant for the entire 1-year period between 2 adjacent visits; if, for example, a participant was taking HCQ at the first and second visits but not at the third visit, then they were considered an HCQ user during the period between the first and third visits (approximately 2 years) and a nonuser from the third visit on (unless HCQ was reintroduced, which qualified as part of our outcome of interest). However, in sensitivity analyses, we repeated the primary analysis, reassigning the date that the patients tapered/stopped HCQ (from the first study visit where the reduction/stop was originally recorded) to a date 6 months prior (i.e., half-way between study visits).

Outcome. The primary composite outcome was time to the first of the following events indicating an SLE flare: 1) an increase of at least 4 points (above baseline score) in the SLE Disease Activity Index 2000 (SLEDAI-2K) score; 2) hospitalization for SLE; and/or 3) augmented SLE therapy, defined as an increase in HCQ (or restart if discontinued) or a new start or increase in any of the following: prednisone, immunosuppressive agents (azathioprine, methotrexate, or mycophenolate mofetil), biologics (rituximab or belimumab), cyclophosphamide, or start of chloroquine.

One center (Halifax) was unable to provide information on hospitalizations for 50% of their participants, thus the primary composite outcome for these patients was based on an increase in disease activity and therapy augmentation only. We also performed sensitivity analyses leaving out these patients.

Potential risk factors. Sociodemographic variables included sex, race/ethnicity (White versus Asian, Black, First

Nations, or other), education (high school education or less versus college or university education), and age at SLE diagnosis (dichotomized at ≤ 25 versus > 25 years, to prevent collinearity with disease duration). Other baseline variables included body mass index (continuous), currently smoking (yes versus no), SLE duration (continuous), disease activity (≥ 4 points in SLEDAI-2K score, which is a validated definition of active SLE) (12,13), time taking HCQ since study enrollment (continuous), use of prednisone, immunosuppressive agents (azathioprine, methotrexate, or mycophenolate mofetil), and biologic agents (rituximab or belimumab), and the presence of renal damage based on the Systemic Lupus International Collaborating Clinics (SLICC) damage index (i.e., scores for heavy proteinuria and/or reduced glomerular filtration rate, or end-stage renal failure) (14).

Statistical analysis. Crude event rates and 95% confidence intervals (95% CIs) were calculated for the primary composite outcome (i.e., the earliest event indicating an SLE flare). We used multivariable Cox proportional hazards regression to estimate the adjusted hazard ratios (HR_{adj}) and 95% CIs for the associations between patient characteristics and the primary outcome. The proportional hazards assumption was verified using the cumulative sums of Martingale residuals and the

Kolmogorov-type supremum test. Multicollinearity was assessed using collinearity indices, eigenvalues, and variable decomposition proportions.

We performed several secondary analyses. First, we repeated the primary analysis separately for each specific component of the composite outcome (i.e., increase in disease activity, SLE-related hospitalizations, and therapy augmentation), while censoring patients who had one of the other events prior to the component of interest. Second, as mentioned before, we conducted sensitivity analysis reassigning the date that the patients tapered/stopped HCQ from the first study visit where the reduction/stop was originally recorded to a date half-way between study visits. Third, we also conducted a sensitivity analysis removing patients without hospitalization data (Halifax) from the primary analysis.

Finally, we compared all results with a third cohort of patients with SLE: those who did not reduce or stop HCQ. The purpose here was to explore whether risk factors influenced the outcome even when HCQ dose was unchanged or whether risk factors were specific among those who decreased or interrupted HCQ treatment. Since the date of taper/discontinuation was used as time zero in our first 2 cohorts, time zero in the third cohort (HCQ maintenance) was defined

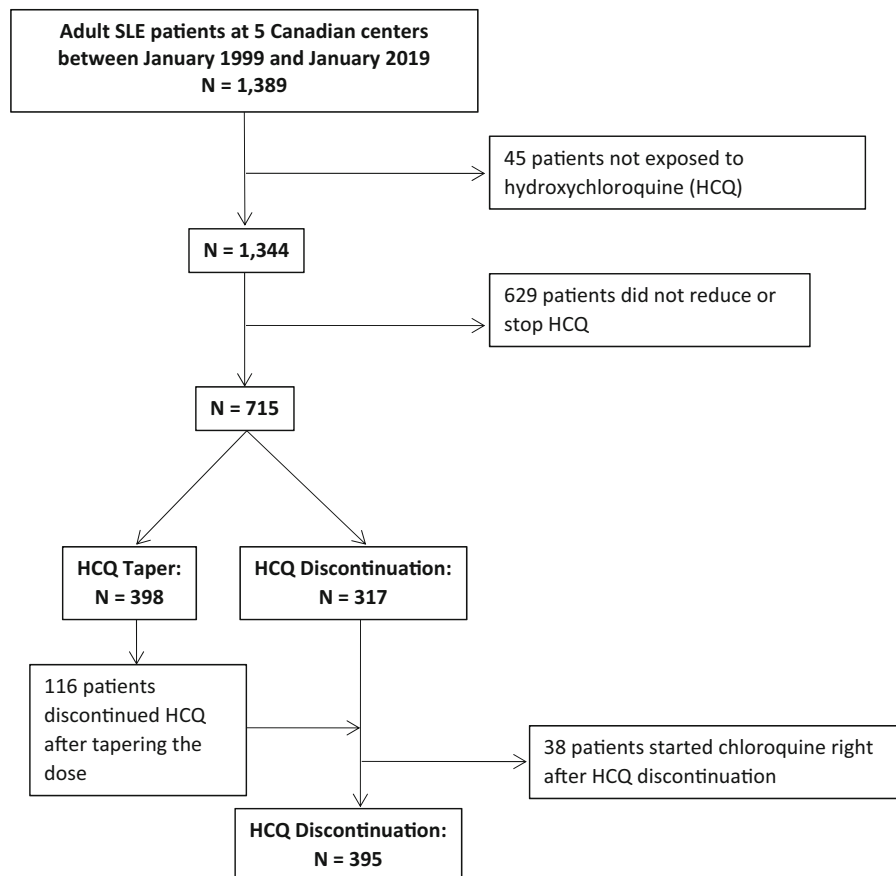


Figure 1. Cohort selection. SLE = systemic lupus erythematosus.

Table 1. Baseline characteristics of patients with SLE tapering, discontinuing, or maintaining HCQ*

Characteristic	Taper (n = 398)	Discontinuation (n = 395)	Maintenance (n = 395)
Female	368 (92.5)	361 (91.4)	347 (87.8)
Race/ethnicity			
White	297 (74.6)	307 (77.7)	295 (75.3)
Asian	55 (13.8)	32 (8.1)	33 (8.4)
Black	31 (7.8)	37 (9.4)	35 (8.9)
First Nations	9 (2.3)	16 (4.0)	20 (5.1)
Others†	6 (1.5)	3 (0.8)	9 (2.3)
Age at SLE diagnosis, years			
Median (IQR)	30.6 (23.2–41.8)	31.9 (24.1–42.0)	32.4 (22.1–46.4)
Age ≤25 years	129 (32.4)	114 (28.9)	127 (32.2)
Age at time zero, median (IQR) years	43.7 (33.5–55.4)	48.5 (37.4–59.0)	46.6 (34.1–57.8)
No college/university education	110 (28.1)	113 (30.1)	85 (22.6)
Center			
Montreal	224 (56.3)	202 (51.1)	109 (27.6)
Halifax	76 (19.1)	84 (21.3)	100 (25.3)
Calgary	45 (11.3)	17 (4.3)	49 (12.6)
Winnipeg	32 (8.0)	83 (21.0)	72 (18.2)
Quebec	21 (5.3)	9 (2.3)	65 (16.5)
SLE duration, median (IQR) years	7.9 (3.6–16.6)	12.9 (6.4–20.6)	6.4 (4.1–17.1)
Disease activity			
Median SLEDAI-2K score (IQR)	2.0 (0.0–6.0)	1.0 (0.0–4.0)	2.0 (0.0–4.0)
SLEDAI-2K score ≥4	186 (46.7)	125 (31.6)	159 (40.2)
Renal damage	30 (7.5)	36 (9.1)	29 (7.3)
Current smoker	150 (37.7)	145 (36.7)	98 (24.8)
Body mass index, median (IQR) kg/m ²	24.4 (21.7–28.3)	25.4 (22.5–30.1)	25.4 (22.1–30.3)
Current prednisone	79 (19.8)	42 (10.6)	103 (26.1)
Current immunosuppressors‡	144 (36.2)	76 (19.2)	176 (44.6)
Current biologic agents‡	17 (4.3)	6 (1.5)	9 (2.3)
Time on HCQ, median (IQR) years§	2.3 (1.2–4.5)	3.0 (1.2–6.1)	1.6 (1.0–3.1)

* Values are the number (%) unless indicated otherwise. HCQ = hydroxychloroquine; IQR = interquartile range; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

† Arab peoples and those of mixed ethnicity.

‡ Immunosuppressors included mycophenolate, azathioprine, and methotrexate; biologics included belimumab and rituximab.

§ Since study entry.

as the visit date when both SLE duration and time taking HCQ individually matched the respective baseline values of patients tapering/discontinuing HCQ. Since patients in the HCQ taper and discontinuation cohorts could not enter that cohort unless they had had at least 2 visits (one visit with baseline HCQ and the second visit when HCQ was tapered/stopped), we also required at least 2 visits for patients in the HCQ maintenance cohort. Statistical analyses were performed using SAS software, version 9.4.

RESULTS

Among 1,389 individuals receiving care in the participating lupus clinics between January 1999 and January 2019, 1,344 (96.8%) were exposed to HCQ (Figure 1). We identified 398 patients (1,740 person-years) who reduced the HCQ dose, and 395 (2,120 person-years) who discontinued HCQ. Among those who maintained HCQ therapy (n = 629), 395 patients (792 person-years) were successfully matched to patients tapering or discontinuing HCQ therapy on previous disease duration

and time on HCQ. Overall, a total of 240 patients were lost to follow-up, 62 withdrew consent, and 35 died during the follow-up. All these patients were censored at the corresponding times.

The baseline characteristics of each of the 3 cohorts of patients with SLE are shown in Table 1. As expected, approximately 90% of the participants were female, and most were White. The primary composite outcome occurred in 261 of the 398 patients who tapered HCQ (35.7 events per 100 person-years [95% CI 31.6–40.3]), in 226 of the 395 patients who discontinued HCQ (29.0 per 100 person-years [95% CI 25.5–33.0]), and in 97 of the 395 patients who remained on HCQ (16.1 events per 100 person-years [95% CI 13.2–19.6]).

The most common poor outcome was therapy augmentation (52.8% after tapering, 48.9% after stopping HCQ, and 17.2% in those maintaining HCQ), followed by SLEDAI-2K score increase of ≥4 points (19.4% after tapering, 20.2% after stopping HCQ, and 10.3% in those maintaining HCQ) and hospitalization for SLE (0.8% after tapering, 0.6% after stopping HCQ, and 0.3% in those maintaining HCQ).

Table 2. Cox regression analysis: baseline characteristics and the primary outcome (earliest poor outcome)*

Baseline characteristic	HCQ taper (n = 398)		HCQ discontinuation (n = 395)		HCQ maintenance (n = 395)	
	HR (95% CI)	HR _{adj} (95% CI)†	HR (95% CI)	HR _{adj} (95% CI)†	HR (95% CI)	HR _{adj} (95% CI)†
Male	1.22 (0.73–2.03)	1.40 (0.83–2.37)	0.60 (0.34–1.06)	0.65 (0.36–1.15)	0.65 (0.31–1.34)	0.52 (0.23–1.19)
Race/ethnicity (vs. White)						
Asian	1.26 (0.87–1.84)	1.14 (0.76–1.72)	1.12 (0.65–1.94)	1.04 (0.58–1.89)	2.05 (0.94–4.47)	1.33 (0.54–3.25)
Black	1.37 (0.90–2.09)	1.03 (0.65–1.65)	1.79 (1.20–2.67)‡	1.61 (1.03–2.51)‡	1.49 (0.69–3.24)	1.29 (0.56–2.97)
First Nations	0.76 (0.24–2.38)	0.75 (0.23–2.40)	1.19 (0.56–2.54)	0.90 (0.40–2.03)	2.81 (1.34–5.86)‡	2.87 (1.21–6.76)‡
Others	0.42 (0.10–1.69)	0.35 (0.09–1.44)	3.22 (0.79–13.0)	2.01 (0.47–8.54)	1.71 (0.24–12.4)	1.44 (0.16–12.9)
Age ≤25 years at SLE diagnosis	1.29 (0.99–1.67)	1.22 (0.92–1.62)	1.61 (1.22–2.13)‡	1.75 (1.29–2.38)‡	1.37 (0.91–2.07)	1.18 (0.73–1.91)
No college/university education	0.97 (0.74–1.26)	0.92 (0.69–1.22)	1.10 (0.83–1.45)	1.18 (0.87–1.60)	0.77 (0.47–1.25)	0.86 (0.49–1.49)
SLE duration, years	1.00 (0.99–1.01)	1.00 (0.99–1.02)	0.99 (0.98–1.01)	1.00 (0.98–1.01)	0.99 (0.96–1.01)	0.99 (0.96–1.02)
SLEDAI-2K score ≥4	1.23 (0.96–1.57)	1.16 (0.89–1.50)	1.08 (0.82–1.42)	1.01 (0.74–1.36)	1.33 (0.88–2.01)	1.10 (0.70–1.73)
Baseline renal damage	1.30 (0.86–1.99)	1.04 (0.65–1.67)	1.05 (0.69–1.59)	0.84 (0.52–1.35)	1.12 (0.45–2.75)	1.32 (0.51–3.44)
Body mass index, kg/m ²	1.01 (0.99–1.04)	1.02 (0.99–1.04)	1.02 (0.99–1.04)	1.01 (0.98–1.03)	0.99 (0.96–1.03)	0.98 (0.95–1.02)
Smoker at baseline	0.71 (0.56–0.92)‡	0.81 (0.61–1.07)	0.62 (0.47–0.82)‡	0.66 (0.49–0.89)‡	0.71 (0.46–1.10)	0.88 (0.52–1.50)
Baseline prednisone	1.84 (1.34–2.53)‡	1.74 (1.23–2.45)‡	1.30 (0.88–1.91)	1.16 (0.72–1.87)	1.40 (0.89–2.19)	1.00 (0.58–1.71)
Baseline immunosuppressors	1.19 (0.92–1.53)	1.06 (0.80–1.41)	1.04 (0.76–1.42)	0.93 (0.64–1.33)	1.90 (1.27–2.85)‡	1.72 (1.08–2.71)‡
Baseline biologics	1.06 (0.56–2.00)	0.89 (0.45–1.75)	2.46 (0.78–7.72)	2.20 (0.64–7.52)	2.36 (0.96–5.83)	1.54 (0.55–4.29)
Time receiving HCQ, years	0.99 (0.95–1.04)	1.00 (0.96–1.05)	0.97 (0.93–1.00)	0.98 (0.94–1.01)	0.86 (0.76–0.97)‡	0.89 (0.78–1.01)

* Baseline medication use represents whether or not patients were taking the drug at time zero. 95% CI = 95% confidence interval; HCQ = hydroxychloroquine; HR = hazard ratio; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

† Variables adjusted concomitantly for all others.

‡ Statistically significant.

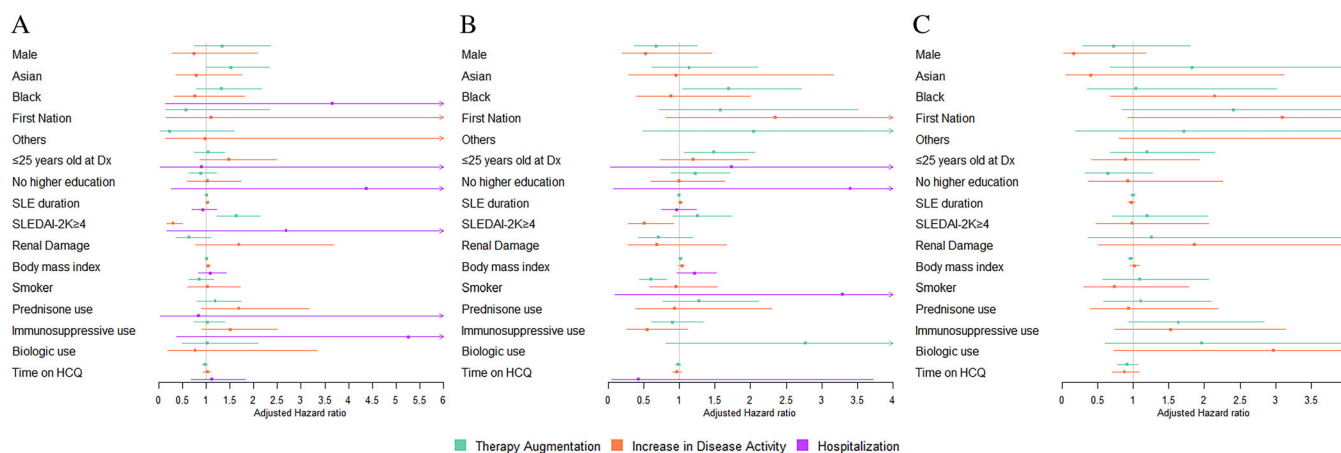


Figure 2. Forest plot showing associations between baseline characteristics and each secondary outcome among patients: **A**, hydroxychloroquine (HCQ) tapering; **B**, HCQ discontinuation; and **C**, HCQ maintenance. Baseline medication use represents whether patients were taking the drug at time zero. Variables are adjusted concomitantly for all others. Omitted lines indicate that no event occurred among exposed patients. Dx = diagnosis; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 2 shows associations between patients' baseline characteristics and the earliest poor outcome. In multivariable analyses, patients using prednisone at time zero had an increased risk of experiencing a poor outcome after HCQ was tapered. After discontinuing HCQ, Black patients, those diagnosed with SLE at a younger age (≤ 25 years), and nonsmokers had a higher risk of a poor outcome. None of these factors were clearly associated with the composite outcome among those maintaining HCQ, although First Nations ethnicity and baseline immunosuppressive use were.

Evaluations of each outcome separately are shown in Figure 2. Asian patients (HR_{adj} 1.52 [95% CI 0.99–2.32]) and those with active disease (HR_{adj} 1.62 [95% CI 1.22–2.14]) at the time of HCQ taper were more likely to need therapy augmentation (Figure 2A). In the HCQ discontinuation cohort, Black race/ethnicity (HR_{adj} 1.69 [95% CI 1.05–2.71]), younger age at SLE diagnosis (HR_{adj} 1.48 [95% CI 1.07–2.06]), and nonsmoking (HR_{adj} 0.59 [95% CI 0.43–0.82]) were predictors of therapy augmentation (Figure 2B). Patients with baseline SLEDAI-2K score ≥ 4 were less likely to have a subsequent increase in disease activity after HCQ was tapered or discontinued. We did not identify clear predictors of any separate outcome among patients who maintained HCQ (Figure 2C). No clear associations were observed between patients' characteristics and SLE-related hospitalization, possibly because statistical power was limited due to the relatively low number of hospitalizations.

The results of sensitivity analyses where we reassigned the date that the patients tapered/stopped HCQ from the first study visit where the reduction/stop was originally recorded to a date 6 months prior (i.e., half-way between study visits) were consistent with the primary analyses (see Supplementary Table 1, available on the *Arthritis Care & Research* website at [http://](http://onlinelibrary.wiley.com/doi/10.1002/acr.24548)

onlinelibrary.wiley.com/doi/10.1002/acr.24548), as were the results leaving patients without hospitalization information out from the analysis (see Supplementary Table 2).

DISCUSSION

Although our study was originally motivated by the desire to better understand personalized therapy in SLE, our findings take on new importance in the current setting, where physicians and patients may face shortages of HCQ, due to interest in this drug as a potential therapy for COVID-19. Although current evidence shows that HCQ is not effective for COVID-19, patients in many countries, including the US, Brazil, and India, are still using HCQ to prevent or treat the infection. In addition, HCQ shortages may occur in other circumstances, such as the prolonged manufacturing shortage faced by the US in 2015 (15). Moreover, stopping HCQ by choice is not that rare; studies have shown that over 30% of patients with SLE discontinue HCQ by choice (7,16).

In this clinical cohort of patients with SLE exposed to HCQ, we observed that multiple demographic and baseline clinical factors are associated with poor outcomes, such as an increase in disease activity and a need for therapy augmentation, after HCQ taper/discontinuation. Tapering HCQ in Asian patients with SLE or when the patient is still on prednisone or with a SLEDAI-2K score of ≥ 4 may result in poorer outcomes. Discontinuing HCQ may be associated with poorer outcomes in Black patients with SLE, and patients age ≤ 25 years at SLE diagnosis. None of these factors were associated with the outcome among those maintaining HCQ, although First Nations patients and baseline immunosuppressive use were.

We did not aim to compare the 3 cohorts directly in terms of flare rate. However, the crude flare rate was significantly lower in the HCQ maintenance cohort (16.1 events per 100 person-years

[95% CI 13.2–19.6]) than in the taper cohort (35.7 [95% CI 31.6–40.3]) and in the discontinuation cohort (29.0 [95% CI 25.5–33.0]). Of course, these crude rates do not consider the fact that variables like disease activity and concomitant medications may differ considerably between the cohorts. If patients tapered or discontinued HCQ solely because of inactive disease, we would expect lower outcome rates in the taper than in the discontinuation group. However, reasons for lowering the dose or discontinuing a medication are multifactorial and may have included patient tolerance, adherence, or even changes in guidelines, including the 2016 American Academy of Ophthalmology (AAO) recommendations, which cautioned against cumulative use of HCQ and lowered dosing to 5 mg/kg per day (5). Thus, not all patients were in remission when HCQ was tapered or discontinued. In fact, we observed that the proportion of patients with active disease (SLEDAI-2K score ≥ 4) at baseline was higher in the HCQ taper cohort (46.7% [95% CI 41.8–51.6]) than in the discontinuation cohort (31.6% [95% CI 27.0–36.2]). Given this finding, the relatively high number of patients in the taper group with a poor outcome makes sense. The fact that the maintenance group had higher baseline disease activity (and more use of immunosuppressives, corticosteroids, and biologics) than the discontinuation group, but a significantly lower (not higher) flare rate, suggests that HCQ is beneficial in this group.

Prednisone is a marker of more severe and active SLE (17,18). In our sample, among patients using prednisone while tapering HCQ, 60.8% (95% CI 49.9–71.6) had active SLE, compared with 43.3% (95% CI 37.8–48.7) not taking prednisone. A baseline SLEDAI-2K score of ≥ 4 was also identified as a predictor of therapy augmentation among patients tapering HCQ. These findings confirm a clinical intuition that patients with active disease are more likely to have poor outcomes, especially a need for therapy augmentation.

Among patients who remained on HCQ, immunosuppressive use was associated with our composite outcome (i.e., the earliest poor outcome). Immunosuppressors are also a marker of more severe disease (19,20). However, we did not find significant interactions between prednisone or immunosuppressors and disease activity in relation to our outcomes. Although multicollinearity between baseline prednisone, immunosuppressors, and SLEDAI-2K score could theoretically be an issue, diagnostic tests showed no threat of multicollinearity in our multivariate models.

In both tapering and discontinuation cohorts, we observed a negative association between a baseline SLEDAI-2K score of ≥ 4 and the specific outcome related to “increase in SLEDAI-2K score.” This finding may represent a ceiling effect of the SLEDAI-2K assessment tool (21,22), which prevented the detection of a worsening in disease activity in patients with a baseline SLEDAI-2K score of ≥ 4 , and/or a regression toward the mean, where more active patients with SLE may get better over time, and less active patients may get worse.

Non-White patients were more likely than White patients to have poor outcomes in all 3 cohorts. This finding was especially true in Black patients discontinuing HCQ, Asian patients tapering HCQ, and First Nations patients remaining on HCQ. Non-White patients, especially Black and First Nations patients, not only may have more severe SLE due to innate disease characteristics, but may also face barriers to optimal health outcomes, including access to care issues (even in the context of Canada’s comprehensive health care system, which does not cover the cost of out-of-hospital medications for all individuals) and poor medication adherence (23,24). In general, non-White patients with SLE may have poorer outcomes due to sociocultural and psychosocial issues (25,26), including a higher risk for flares (27). As mentioned before, patients possibly discontinued the drug against physician advice; those patients may also have been nonadherent with other medications and physician advice, which could explain the findings of higher flare risk with Black patients who discontinued HCQ.

The risk of a poor outcome after HCQ discontinuation was higher in patients with SLE diagnosed at age ≤ 25 years. Younger SLE onset is generally more driven by genetic factors, which may correspond to a more severe SLE phenotype (28). Previous studies also identified younger age at SLE diagnosis as a strong predictor of lupus flares (20,27,29), including pediatric-onset SLE (30). At the same time, treatment toxicity (primarily retinal) has the potential to accumulate over a long period (30), which creates difficulty balancing the risks and benefits of long-term HCQ use.

We observed that baseline current smoking was inversely associated with poor outcomes after HCQ discontinuation, a finding that was not apparent in adjusted analyses of HCQ tapering or maintenance. Antimalarials are known to have decreased efficacy among smokers (31), probably due to tobacco’s effect on the cytochrome P-450 enzyme system (32). Indeed, we observed that smokers already had worse disease activity at baseline than nonsmokers (data not shown). Thus, discontinuation of HCQ in smokers may not have the same clinical impact as in nonsmokers. On the other hand, since we did not update smoking status over time, some of those patients who smoked at the time of HCQ discontinuation may have stopped smoking, whereas very few of the nonsmokers would have started smoking over time. This nondifferential misclassification of smoking exposure may have contributed to the unexpected inverse relationship between smoking and poor outcomes (particularly if stopping smoking was associated with other nonmeasured variables, such as adherence to other medications).

We acknowledge important potential limitations in the current study. First, due to its exploratory nature, we did not adjust our analyses for multiple comparisons (33). Therefore, subsequent research with preplanned hypotheses should be conducted to confirm the observed associations. Second, data on HCQ use before the beginning of the study were not available, and the variable “time on HCQ” was calculated using the study

entry date, which may underestimate the real time of exposure. We estimate that the real duration of HCQ may be approximately 2 years less than SLE duration, since patients usually start HCQ therapy 2 years after SLE diagnosis. Third, we do not know for sure the reasons for reducing the dose or discontinuing HCQ. Therefore, drawing conclusions about effectiveness of HCQ by comparing the 3 cohorts is not possible, although patients remaining on HCQ had a significantly lower outcome rate than those tapering or discontinuing HCQ. In addition, although the identified demographic and baseline factors are warning signs of patients who might not do well on a taper/discontinuation independently of the reason, the reason for tapering/stopping HCQ may influence later flare risk and/or the reason for subsequent therapy augmentation. As mentioned before, HCQ tapering may have occurred because the patient was doing well (stable disease), or because the physician was following the 2016 AAO recommendations. HCQ discontinuation, on the other hand, may be due to retinal toxicity or the patient's choice (nonadherence), besides the cases where patients were in prolonged disease remission.

To exclude the possibility that the reasons for tapering/stopping HCQ may be biasing our results, we evaluated the effects of the calendar year, considering the date that the AAO guideline was published, and retinal damage in the respective cohorts. Among patients tapering HCQ, 30% had their dose reduced after the AAO guideline was published, and the inclusion of the calendar year variable in the multivariable model for the taper cohort did not yield different estimations. Similarly, among those stopping HCQ, 8% had retinal damage (identified using the SLICC damage index) at baseline, and adjusting for it did not change the multivariable model. Although we did not evaluate adherence, by adjusting the analyses for sex, age, race/ethnicity, and multiple medications, we accounted for factors that are themselves strong predictors of adherence in SLE. At Canadian centers, measurements of HCQ levels are not part of usual care and are rarely obtained. Nevertheless, the literature indicates that approximately 30% of patients with SLE are nonadherent to HCQ treatment (7,16), so most patients with active disease at baseline who stopped HCQ probably did so on their own (possibly due to side effects or other concerns), since physicians do not commonly discontinue treatment in patients with active SLE.

Our multivariate analyses suggested that prednisone use and a SLEDAI-2K score of ≥ 4 at the time of HCQ tapering were associated with a greater risk of a poor outcome, as was Asian race/ethnicity. Among those discontinuing HCQ, the risk of a poor outcome was greater for Black patients and those diagnosed with SLE at age ≤ 25 years. In patients who maintained HCQ therapy, baseline immunosuppressive use and First Nations ethnicity were associated with poor outcomes. The identification of multiple demographic and clinical predictors of poor outcomes after HCQ taper/discontinuation may be useful in personalizing decisions for patients with SLE (and their physicians) around

medication de-escalation or maintenance, as well as monitoring for flares when HCQ tapering or stopping is needed, such as in the current setting of potential HCQ shortages due to interest in this drug as a therapy for COVID-19.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bernatsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Pineau, Vinet, Hanly, Peschken, Clarke, Fortin, Abrahamowicz, Bernatsky.

Acquisition of data. Pineau, Vinet, Hanly, Peschken, Clarke, Fortin, Bernatsky.

Analysis and interpretation of data. Almeida-Brasil, Abrahamowicz, Bernatsky.

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