The Association of Hydroxychloroquine Dosing with Adverse Cardiovascular Events In Patients with Systemic Lupus Erythematosus

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BACKGROUND AND OBJECTIVES

- Guidelines recommend starting HCQ at the time of SLE diagnosis at a dose <=5mg/kg based solely on the increased risk of retinopathy with higher doses.
- SLE is associated with a significant risk of cardiovascular disease
- Both harmful and protective effects of HCQ on cardiovascular health have been reported
- The influence of HCQ dose in the balance between protective and toxic cardiovascular effects is uncertain

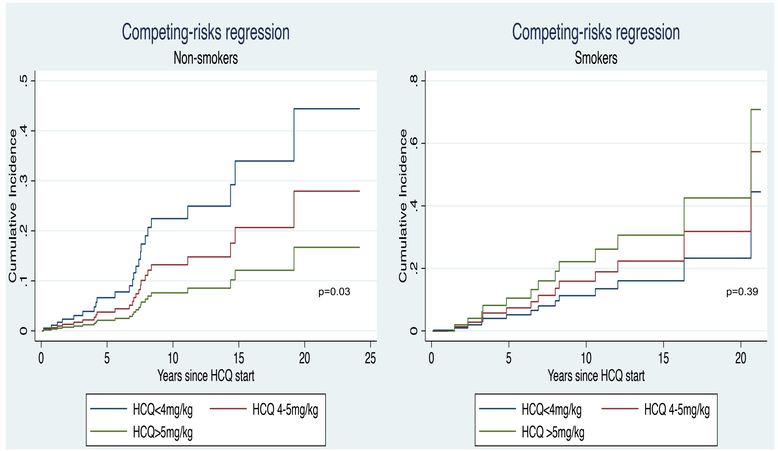
- **Objective:** To determine if HCQ dose is associated with all-cause heart failure with reduced ejection fraction (HFrEF), life-threatening arrhythmia or cardiac death in SLE

METHODS

- Retrospective cohort study in a tertiary care center in New York between years 2005 and 2021
- Inclusion criteria: ACR/SLICC criteria for SLE, started on HCQ, at least 1 echocardiogram on file. Patients that never took HCQ were excluded.
- Outcome: first occurrence of HFrEF, ventricular arrhythmia or complete heart block, need for defibrillator placement or pacemaker, or cardiac death.
- Primary exposure of interest: baseline HCQ-weight based dose
- Secondary exposure: averaged weight based doses over time.
- We used competing risk regression to study the association of HCQ dose with the composite outcome. Competing risk: non-cardiac deaths.
- An interaction with smoking was detected (p=0.02). Separate models were fit for smokers and non-smokers

RESULTS

- A total of 38/296 (13%) patients developed the outcome over a median (IQR) follow up time of 7.0 (3.3,11.8) years.
- Mean age at baseline (HCQ start date) was 33 ± 13.6 years. A total of 267 (90%) were female and 278 (94%) self-identified as Hispanic or Black.
- At baseline, 97 (33%) had lupus nephritis, 44 (15%) had chronic kidney disease stage 3 or higher, 26 (9%) had a history of thromboembolism or antiphospholipid syndrome, 101 (34%) had hypertension, 68 (23%) were smokers, 11 (4%) had diabetes and 7 (2%) had coronary artery disease.
- Mean HCQ weight-based dose was 5.2 ± 1.5 mg/kg at baseline and 5.1 ± 1.5 in average through follow up. Median (IQR) HCQ duration and cumulative dose were 6.5 (3.1, 11.3) years and 828 (328, 1467) grams, respectively.



Competing Risk Regression Analysis

	Non-smokers n=225				Smokers n=67			
	Unadjusted SHR (95% CI)	**p**	**Adjusted* SHR (95% CI)**	**p**	**Unadjusted SHR (95% CI)**	**p**	**Adjusted** SHR (95% CI)**	**p**
Baseline Doses								
HCQ weight-based dose, per mg/kg	0.76(0.57,1.0)	0.05	0.72(0.53,0.98)	0.03	1.12(0.82,1.53)	0.47	1.12(0.77,1.65)	0.56
HCQ mg/kg categories								
<4mg/kg	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
4-5mg/kg	0.23(0.06,0.83)		0.27(0.08, 0.94)		2.39(0.43,13.3)		2.63(0.33, 20.64)	
>5mg/kg	0.32(0.14,0.75)		0.3(0.11,0.83)		2.31(0.43, 12.3)		2.58(0.32,21.02)	
p for trend		0.02		0.03		0.33		0.39
Average Doses								
HCQ average weight-based dose, per mg/kg	0.69(0.51,0.93)	0.01	0.72(0.52,1.0)	0.05	1.1(0.80, 1.52)	0.55	1.09(0.77,1.56)	0.62
HCQ average mg/kg categories								
<4mg/kg	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
4-5mg/kg	0.71(0.27,1.87)		0.59(0.2, 1.78)		1.05(0.21,5.18)		1.06(0.21,5.34)	
>5mg/kg	0.36(0.12,0.96)		0.43(0.15,1.21)		1.70(0.46, 6.34)		1.69(0.45,6.38)	
p for trend		0.03		0.1		0.4		0.4

*Models adjusted for age, chronic kidney disease, thromboembolism and diabetes
** Shown models adjusted for age

CONCLUSIONS

- There is a 28% reduction in the the risk of HFrEF, life-threatening arrhythmia or cardiac death per mg/kg of HCQ among non-smokers.
- No significant association was seen between HCQ weight-based dose and the outcome among smokers. Smoking is known to interfere with the effect of HCQ.
- The risk reduction of the outcome among non-smokers, might be related to a positive dose-dependent impact of HCQ on underlying conditions such as coronary artery disease, microvascular dysfunction and prothrombotic states. Better SLE disease control is also possible.
- If confirmed with future studies, these results would support the inclusion of the potential cardiovascular benefits derived from higher HCQ dosing into HCQ dosing risk-benefit considerations, beyond the risk for retinopathy

STRENGHTS AND LIMITATIONS

Strengths:
- Longitudinal design with long follow-up
- Findings in concordance with literature on other connective tissue diseases
- A mechanism to explain the findings exists
- Study is reflective of real-world clinical experience

Limitations:
- Retrospective single-center design
- Residual confounding
- Included only patients with available ECHO: generalizability
- Cardiac serological markers or HCQ levels not available, adherence not accounted for.

REFERENCES

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