

Canadian Rheumatology Association Position Statement on the Safety of Hydroxychloroquine in the Treatment of Rheumatic Diseases

Version: 2.0 December 3, 2024

Highlights of changes:

Updated to include:

- Monitoring recommendations for hydroxychloroquine ocular toxicity
- Reassurance for the usual therapeutic dose of hydroxychloroquine used in rheumatology (in light of the COVID -19 pandemic and reported cardiac toxicities with the use of anti-malarial drugs)

The antimalarial drugs, chloroquine and especially hydroxychloroquine (HCQ), are essential drugs in the treatment of rheumatic diseases. HCQ is currently the only anti-malarial drug available in Canada for the treatment of rheumatic diseases. HCQ is important in the management of systemic lupus erythematosus (SLE) (1,2). It has been shown to improve survival (3,4,5) and prevent disease flares (6,7). Other important benefits in SLE include reducing organ damage (15), lowering cholesterol (8,9,10), improving glucose metabolism (11,12), decreasing thromboembolic (13) and cardiovascular events (14) and improves pregnancy outcomes for mother and fetus in SLE (16). HCQ is also important in the treatment of rheumatoid arthritis (RA) and is one of the more commonly prescribed disease-modifying antirheumatic drugs (17,18).

As with all medications, HCQ use requires monitoring. Retinal toxicity is an important potential side effect encountered (19,20). Retinopathy is irreversible, so early recognition through regular monitoring is important to prevent permanent vision loss. The American Academy of Ophthalmology recommends fundus screening with visual fields plus spectral-domain optical coherence tomography (OCT) at baseline and after 5 years of treatment (36). Major risk factors include duration of use, renal disease, and concomitant tamoxifen. A baseline fundus examination should be performed to rule out pre-existing maculopathy and annual screening should begin after 5 years of use in patients without major risk factors (21).

Skin hyperpigmentation (22), myopathy (23,24), including cardiomyopathy (25,26), are other uncommon side effects. Nonetheless, HCQ is considered one of the safest drugs used by the rheumatologist. Data from a rheumatic disease registry found that in evaluating the relative toxicity of several drugs used in rheumatology, HCQ was the least toxic of the drugs studied (27).

With the COVID-19 pandemic, cardiac toxicity was reported with the use of antimalarial drugs (28,29). Concerns were raised about the increased occurrence of QT prolongation leading to serious arrhythmias such as Torsade de Pointes and cardiac arrest (28,29). However, the pandemic resulted in the unconventional use of HCQ (30), frequently at much higher doses than used to treat rheumatic diseases, and often in combination with azithromycin which may further prolong the QT interval (29). In addition, COVID-19 infection itself can cause

arrhythmias and cardiomyopathy (29,31). These patients also commonly had hypokalemia, hypomagnesemia, as well as fever, which can potentiate QT prolongation (31).

With conventional dosing and use, cardiac toxicity has been rarely encountered in rheumatology practice (30). In a study in SLE patients on antimalarials, the prevalence of prolonged QT interval was very low, only 0.7% (32). Others showed that the prevalence of conduction abnormalities in SLE patients on HCQ is similar to a comparable healthy population (33). Possible risk factors for cardiotoxicity in patients receiving antimalarials include older age, pre-existing cardiac disease and renal insufficiency (32).

For the most part, therapeutic doses of hydroxychloroquine for rheumatic diseases will not result in clinically relevant drug interactions. However, HCQ has been associated with prolongation of the QT interval when used in combination with certain medications (34), therefore recognition of significant drug interactions is important. Most anti-depressants (including bupropion, citalopram, escitalopram, duloxetine, fluoxetine, mirtazapine, paroxetine, sertraline, trazodone, and venlafaxine), seem to only mildly prolong QT, within normal ranges, when used concurrently with HCQ and are thus likely safe (31).

The use of HCQ to treat rheumatic diseases is overall felt to be safe when prescribed appropriately and when the patient is monitored and followed by a rheumatologist (30). The significant benefits of HCQ, particularly in SLE, certainly outweigh its risks.

REFERENCES

1. Fanouriakis, A., et al., 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:736-745.
2. Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. *Intern Med J* 2012;42:968-78.
3. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, Garmendia M, Villar I, Martinez-Berriotxo A et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus* 2006;15:577–83.
4. Shinjo SK, Bonfá E, Wojdyla D, Borba EF, Ramirez LA, Scherbarth HR et al. Antimalarial treatment may have a time-dependent effect on lupus survival: data from a multinational Latin American inception cohort. *Arthritis Rheum* 2010;62:855–62.
5. Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM et al . Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007;66 1168–72.
6. Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med*. 1991;324(3):150- 154. doi:10.1056/NEJM199101173240303
7. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;69:20–8.
8. Wallace DJ, Metzger AL, Stecher VJ, Turnbull BA, Kern PA. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. *Am J Med* 1990;89:322–6.

9. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med* 1994;96:254–9.
10. Tam LS, Gladman DD, Hallett DC, Rahman P, Urowitz MB. Effect of antimalarial agents on the fasting lipid profile in systemic lupus erythematosus. *J Rheumatol* 2000;27:2142–5.
11. Petri M. Hydroxychloroquine use in the Baltimore lupus cohort: effects on lipids, glucose and thrombosis. *Lupus* 1996;5:S16–22.
12. Penn SK, Kao AH, Schott LL, Elliott JR, Toledo FG, Kuller L et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 2010;37:1136–42.
13. Jung H, Bobba R, Su J, Shariati-Sarabi Z, Gladman DD, Urowitz M et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum* 2010;62:863–8.
14. Nikpour M, Urowitz MB, Ibanez D, Harvey PJ, Gladman DD. Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther* 2011;13:R156.
15. Pons-Estel GJ, Alarcón GS, McGwin G Jr, Danila MI, Zhang J, Bastian HM et al. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Care Res* 2009;61:830–9.
16. Buchanan, N.M., et al., A study of 100 high risk lupus pregnancies. *Am J Reprod Immunol* 1992;28:192-4.
17. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. *J Rheumatol* 2012 Aug; 39(8):1559-82.
18. Singh JA, Saag KG, Bridges SL Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016; 68(1): 1-26.
19. Michaelides M, Stover NB, Francis PJ, Weleber RG. Retinal toxicity associated with hydroxychloroquine and chloroquine: risk factors, screening, and progression despite cessation of therapy. *Arch Ophthalmol* 2011;129:30-9.
20. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010;62:775- 84.
21. Marmor M, Kellner U, Lai T, Melles R., et al. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *American Academy of Ophthalmology* 2016;123:1386-1394.
22. Jallouli M, Francès C, Piette JC, Huong DL, Moguelet P, Factor C, et al, Plaquenil LUPus Systemic Study Group. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: a case-control study. *JAMA Dermatol* 2013 Aug;149(8):935-40.
23. Siddiqui AK, Huberfeld SI, Weidenheim KM, Einberg KR, Efferen LS: Hydroxychloroquine-induced toxic myopathy causing respiratory failure. *Chest* 2007; 131: 588-90.
24. Casado E, Gratacos J, Tolosa C et al.: Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. *Ann Rheum Dis* 2006; 65: 385-90.
25. Yogasundaram H, Putko BN, Tien J et al. Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014;30:1706-15.
26. Cotroneo J, Sleik KM, Rene Rodriguqz E, Klein AL: Hydroxychloroquine-induced restrictive cardiomyopathy. *Eur J Echocardiogr* 2007;8:247-51.
27. James F. Fries, Catharine A. Williams, Dena Ramey and Daniel A Bloch. The relative toxicity of Disease-Modifying Antirheumatic Drugs. *Arthritis Rheum* 1993;36(3):297-306.
28. Tleyjeh IM, Kashour Z, AlDosary O, Riaz M, Tlayjeh H, Garbati MA, Tleyjeh R, Al-Mallah MH et al. The Cardiac Toxicity of Chloroquine or Hydroxychloroquine in COVID-19 Patients: A Systematic Review and Meta-regression

- Analysis. Mayo Clin Proc Innov Qual Outcomes. 2020 Nov 2. doi: 10.1016/j.mayocpiqo.2020.10.005 [Epub ahead of print]
29. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. *Heart Rhythm* 2020;1–8. doi: 10.1016/j.hrthm.2020.05.008 [Epub ahead of print]
30. Touma Z. HCQ and the Heart. *CRAJ* 2020;30(2):29. 4
31. Oren O, Yang EH, Gluckman TJ, Michos ED, Blumenthal RS, Gersh BJ. Use of Chloroquine and Hydroxychloroquine in COVID-19 and Cardiovascular Implications. *CIRC-ARRHYTHMIA ELEC* 2020;13(6):e008688.
32. McGhie TK, Harvey P, Su J, Anderson M, Tomlinson G, Touma Z. Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus. *Clin Exp Rheumatol* 2018;36(4):545-51.
33. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Leroux G, Lechat P, Funck-Brentano C, et al. Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatology (Oxford, England)* 2007;46(5):808-10.
34. Park E, Giles JT, Perez-Recio T, Pina P, et al. [Hydroxychloroquine use is not associated with QTc length in a large cohort of SLE and RA patients.](#) *Arthritis Res Ther.* 2021; 23(1):271. doi: 10.1186/s13075-021-02646-0.
35. Ulrich A. Hydroxychloroquine interactions: ten things to watch for. 2022. <https://www.goodrx.com/hydroxychloroquine/interactions>
35. Renaldi J, Koumpouras F, Dong X et al. [Evaluating the risk of QTc prolongation associated with hydroxychloroquine use with antidepressants in lupus patients with fibromyalgia.](#) *Lupus.* 2021; 30(11):1844-8. doi:10.1177/096120332110345
36. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology.* 2016 Jun 1;123(6):1386–94.