Can We Individualize the Prevention of Hydroxychloroquine-induced Retinopathy?

By Ruud H.J. Verstegen, MD, PhD; and Deborah M. Levy, MD, MS, FRCPC

Patient Case:

A 15-year-old female presents with a two-month history of joint pain and fatigue. Over the past two weeks, she developed a malar rash and, on examination, has a painless palatal ulcer, mild bifrontal alopecia and two swollen joints. Investigations demonstrate lymphopenia, mild anemia and hypocomplementemia. She is anti-nuclear antibody (ANA) positive (high titre) and positive for anti-Sm antibodies. The remainder of her investigations are negative, and a diagnosis of systemic lupus erythematosus (SLE) is made. Hydroxychloroquine (HCQ) is initiated at the first visit following a discussion of possible adverse effects including retinal toxicity. The patient and her caregiver want to know what should be done to prevent retinopathy, given that she may require this medication for many years, if not decades.

Introduction

HCQ, originally used for the treatment and prophylaxis of malaria, has been used in SLE since the early 1950s because of its excellent safety profile and multiple benefits including improved disease control, survival and decreased damage accrual. Long-term HCQ maintenance has been standard of care since the landmark study by The Canadian Hydroxychloroquine Study group demonstrated an increased risk of disease flare after HCQ discontinuation.[1]

Retinopathy

HCQ has a favourable safety profile with gastrointestinal symptoms including decreased appetite, nausea, abdominal pain, and diarrhea commonly cited.[2] Retinopathy following prolonged treatment with chloroquine and hydroxychloroquine was described in 1959 and 1967, respectively.[3,4] It was initially thought to occur rarely, but more recently a prevalence of 7.5% by more sensitive techniques such as spectral-domain optical coherence imaging (SD-OCT) was observed.[5]

HCQ retinopathy is irreversible and specific treatment is currently lacking. Also, severe toxicity at diagnosis can further progress for at least three years after treatment discontinuation, whereas those with early and moderate toxicity generally have no progression.[6] Therefore, annual SD-OCT screening should start five years after treatment initiation, or earlier in the presence of additional risk factors.[7]

Prevention of Hydroxychloroquine-induced Retinopathy

The identification of risk factors has helped to develop strategies for prevention. Melles and Marmor showed that the risk of HCQ retinopathy is associated with higher HCQ doses (>5.0 mg/kg/day [actual body weight]), prolonged treatment duration (>10 years), cumulative HCQ dose, chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2) and concomitant treatment with tamoxifen.[5] Based on these data, the current recommendations are to use a HCQ dose of 5 mg/kg actual body weight per day (no absolute daily maximum).[7,8] At this dose, the risk of HCQ retinopathy is <2% within the first 10 years of treatment.[5] Compared to prior guidelines that recommended a dose of 6.5 mg/kg ideal body weight per day (maximum 400 mg/day), the new dosing regimen results in lower drug exposure in patients with a low-normal BMI, which may decrease treatment efficacy. In contrast, patients with a BMI >25 will have a relatively higher HCQ exposure than before, which has been shown to result in increased HCQ blood concentrations,[9] and thus may increase toxicity. Besides these general dosing recommendations, there is no clear guidance on HCQ dosing for patients with concurrent renal disease and those treated with tamoxifen.[8]

Precision Therapeutics

Therapeutic drug monitoring (TDM) and pharmacogenetic testing (PGx) may allow for treatment individualization and reduce risks for adverse drug reactions, while optimizing treatment efficacy. TDM is the practice where drug concentration measurements in serum or blood are performed to guide pharmacotherapeutic management, whereas PGx guides treatment decisions by identifying targeted genetic variants that are associated with specific clinical outcomes.

Although HCQ concentrations have been studied for at least 30 years, this test has not seen widespread clinical implementation. There is a large variability in the HCQ blood concentrations achieved for a specific dose,[10] which in part can be explained by (partial) non-adherence in combination with the long half-life (i.e., 30-60 days). Garg et al. recently published a meta-analysis of 17 studies that have explored the optimal HCQ blood concentration in SLE.[11] They found a strong association between low HCQ blood concentrations and non-adherence. In addition, among 1,223 individuals, those with HCQ blood concentrations ≥ 750 ng/mL had a 58% lower risk of active disease, as well as a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score that was 3.2 points lower.[11]

In 2020, Petri et al. published their work on the association between HCQ blood concentrations and the development of retinopathy in SLE.[12] Of 537 patients, 23 developed retinopathy (4.3%). Looking at those who had developed retinopathy, more than half had a HCQ blood concentration in the highest tertile (mean >1,177 ng/mL or maximum >1,753 ng/mL). Unfortunately, this study did not relate blood concentration to the time of HCQ administration (i.e., peak, trough).

Although the available studies provide an important basis to further explore the relationship between HCQ dosing, drug disposition, clinical efficacy, and retinopathy risk, there is significant overlap between the HCQ blood concentrations found in patients with and without a favourable outcome, making it difficult to establish a target drug concentration and interpret individual HCQ blood concentrations. In addition, these results cannot be applied to the pediatric population as data are absent in children (i.e., <12 years old), and very limited in adolescents (12-18 years old).

The individual variation in pharmacokinetics as well as an individual sensitivity to develop HCQ retinopathy may be genetically determined. As of yet, pharmacogenomic studies involving this topic are limited, but variants in CYP2D6, CYP2C8, CYP3A4 and CYP3A5 may contribute to individual pharmacokinetic differences and the risk for adverse drug reactions.[13, 14] In addition, one variant in ABCA4 may be protective of HCQ retinopathy.[15]

Conclusion

Hydroxychloroquine is a hallmark SLE treatment that is usually well tolerated. However, irreversible HCQ retinopathy is an important adverse drug reaction that requires optimal efforts at prevention. Recent dosing recommendations may decrease the rate of retinopathy in some patients, but also impact treatment efficacy. TDM and PGx are promising approaches to individualize HCQ treatment in the future; however, currently, insufficient data exist to guide clinical decision making, and prospective studies to demonstrate their role are needed.

Ruud H.J. Verstegen, MD, PhD
Divisions of Clinical Pharmacology & Toxicology and Rheumatology,
The Hospital for Sick Children
Department of Paediatrics,
University of Toronto
Toronto, Ontario

Deborah M. Levy, MD, MS, FRCPC
Division of Rheumatology,
The Hospital for Sick Children
Department of Paediatrics,
University of Toronto
Toronto, Ontario

References:

1. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. N Engl J Med. 1991; 324(3): 150-4.
2. Sanofi-Aventis Canada Inc. Hydroxychloroquine [Product Monograph]. Health Canada: Drug Product Database [Available from: *https://pdf.hres.ca/dpd_pm/00063288.pdf*].
3. Shearer RV, Dubois EL. Ocular changes induced by long-term hydroxychloroquine (plaquenil) therapy. Am J Ophthalmol. 1967; 64(2): 245-52.
4. Hobbs HE, Sorsby A, Freedman A. Retinopathy following chloroquine therapy. Lancet. 1959; 2(7101):478-80.
5. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA ophthalmology. 2014; 132(12):1453-60.
6. Marmor MF, Hu J. Effect of disease stage on progression of hydroxychloroquine retinopathy. JAMA ophthalmology. 2014; 132(9):1105-12.
7. Marmor MF, Kellner U, Lai TY, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016; 123(6):1386-94.
8. Rosenbaum JT, Costenbader KH, Desmarais J, et al. American College of Rheumatology, American Academy of Dermatology, Rheumatologic Dermatology Society, and American Academy of Ophthalmology 2020 Joint Statement on Hydroxychloroquine Use With Respect to Retinal Toxicity. Arthritis rheumatol. 2021; 73(6):908-11.
9. Pedrosa T, Kupa LVK, Pasoto SG, et al. The influence of obesity on hydroxychloroquine blood levels in lupus nephritis patients. Lupus. 2021; 30(4): 554-9.
10. Carmichael SJ, Day RO, Tett SE. A cross-sectional study of hydroxychloroquine concentrations and effects in people with systemic lupus erythematosus. Intern Med J. 2013; 43(5): 547-53.
11. Garg S, Unnithan R, Hansen KE, et al. Clinical significance of monitoring hydroxychloroquine levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2021; 73(5):707-16.
12. Petri M, Elkhalifa M, Li J, et al. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis rheumatol. 2020; 72(3):448-53.
13. Gao B, Tan T, Cao X, et al. Relationship of cytochrome P450 gene polymorphisms with blood concentrations of hydroxychloroquine and its metabolites and adverse drug reactions. BMC medical genomics. 2022; 15(1): 23.
14. Lee JY, Vinayagamoorthy N, Han K, et al. Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis rheumatol. 2016; 68(1):184-90.
15. Grassmann F, Bergholz R, Mändl J, et al. Common synonymous variants in ABCA4 are protective for chloroquine-induced maculopathy (toxic maculopathy). BMC Ophthalmol. 2015; 15:18.