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Adherence to Hydroxychloroquine Dosing Guidelines by Rheumatologists

An Electronic Medical Record–Based Study in an Integrated Health Care System

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Purpose: To study the adherence of rheumatologists to the hydroxychloroquine (HCQ) dosing guidelines established by the American Academy of Ophthalmology in 2011 and 2016.

Design: Retrospective review of electronic medical records (EMRs) in an integrated health care system.

Participants: All rheumatology patients started on HCQ who were seen by a NorthShore ophthalmologist between the years 2009 and 2016.

Methods: Data on patient weights, height, gender, and HCQ dosage were extracted from the EMR. The recommended maximum starting dose was determined using 2 formulas based on ideal or actual body weight.

Main Outcome Measures: The percentage of patients whose dose exceeded the recommended maximum.

Results: A total of 554 patients on HCQ were identified. Some 50% of the patients had been placed on excess initial doses according to the 2011 guidelines, and 47% of the patients had been placed on excess initial doses according to the 2016 guidelines. The introduction of the guidelines had no appreciable effect on HCQ dosing. A separate analysis of all patients currently receiving maintenance HCQ therapy demonstrated excess dosing in 297 of 527 (56%), according to the 2016 guidelines.

Conclusions: Approximately one half of all patients started on HCQ by NorthShore rheumatologists received doses in excess of the recommended maximum, and slightly more than one-half of all patients currently on treatment continue to receive excess doses. Our data suggest that the publication of the consensus guidelines in 2011 had no appreciable effect on HCQ dosing and that transitioning to the 2016 dosing modification is unlikely to change this outcome unless additional steps are taken to improve adherence. *Ophthalmology 2017;■:1–5 © 2017 by the American Academy of Ophthalmology*

Hydroxychloroquine (HCQ) has been a part of Western pharmacotherapy for more than 4 centuries, dating back to its discovery as an antimalarial agent from the Peruvian Andes.[1] At present, it is predominantly used for the treatment of rheumatologic diseases such as rheumatoid arthritis and systemic lupus erythematosus, for which it has recently experienced a renaissance.[2,3] Additional and novel indications for HCQ continue to emerge, including its potential use in cancer therapy.[4]

Hydroxychloroquine has well-known ocular side effects and toxicities, necessitating careful monitoring of all patients on chronic therapy by ophthalmologists. In recent years, solid data have documented its dose-related retinal toxicity[5] in up to 20% of patients after 20 years of intake. In response, the American Academy of Ophthalmology developed dosing and monitoring guidelines in 2011 and 2016 to define high-risk patients and to establish appropriate testing for retinal toxicity.[6–8]

Given its increasing use within the NorthShore University rheumatology patient population, we were interested in analyzing the time trends of HCQ prescriptions and assessing physician adherence (or nonadherence) to the published HCQ dosing guidelines of 2011. In addition, we analyzed the potential impact of the recent dosing modification suggested in the updated 2016 guidelines. We took advantage of our electronic patient data file to perform a retrospective analysis of all patients receiving HCQ since 2009.

Methods

We performed a retrospective review of all patients in the NorthShore University Health System electronic medical records (EMRs). Waivers of informed consent and Health Insurance Portability and Accountability Act authorization were obtained from the Institutional Review Board of NorthShore University Health System. The described research adhered to the tenets of the Declaration of Helsinki.

We searched the EMR for all unique patients who had had at least 1 documented, active outpatient order for HCQ between 2009

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and 2016, and who had been evaluated by a NorthShore staff ophthalmologist during this time period. Patient medical record numbers, HCQ order dates and doses, height, and weight were extracted and entered into a spreadsheet. Maximal HCQ doses were calculated according to guidelines established in 2011, using the formula for the recommended dose of 6.5 mg/kg of ideal body weight.[8] Ideal body weight in kilograms was calculated as follows for men: 50 + 2.3 (height in inches−60) or women: 45.5 + 2.3 (height in inches−60). Maximum HCQ doses also were calculated using the revised 2016 guidelines formula of 5.0 mg/kg of measured weight.[7] Statistical comparisons were performed by chi-square analysis.

Results

Hydroxychloroquine Dosing before and after the Introduction of the 2011 Consensus Guidelines

We identified 554 patients who had been started on HCQ since 2009. Of these, 92 patients were started before the publication of the 2011 guidelines, and 462 patients were started subsequently.

We calculated the percentage of patients who were started on excess HCQ doses, using the formula recommended in the 2011 guidelines. Approximately one half of all patients were started on excess doses. The percentage of patients receiving excess doses before (54.3%) versus after (49.4%) 2011 was similar ($P = 0.381$).

To account for the possibility that physicians might have changed HCQ doses during treatment, we compared starting to maintenance doses 1 year after treatment initiation. We found that a majority (84%) of patients had been maintained on the initial dose. Dose reductions or increases were documented in 7% and 9% of patients, respectively. This finding helps validate our use of the initial HCQ dose in our analysis.

Time Trends in Hydroxychloroquine Dosing

To detect possible time trends, we analyzed starting HCQ doses in 6-month intervals, comparing the original 2011 and the subsequent 2016 dose calculations. Figure 1 demonstrates the percentage of patients receiving excess doses. No major time-dependent changes were observed. Furthermore, the percentage of patients on excess HCQ doses was not substantially affected when we retrospectively applied the updated 2016 dosing guidelines.

Appropriateness of Current Hydroxychloroquine Dosing

We identified 527 patients who are currently receiving HCQ. On the basis of the 2016 dosing guidelines, 44% of the patients are receiving doses within the recommended range, whereas 56% are receiving excess doses. To examine the extent of overdosing, we analyzed the differences between actual and calculated maximal doses for each patient. Figure 2 shows a histogram of the results, displayed in 50-mg increments. A total of 303 of 527 patients (57%) are receiving doses below target or within 50 mg above the target amounts. However, a substantial number of patients (224/527, 43%) are receiving doses that are more than 50 mg in excess of the calculated target, including several patients who are receiving up to 450 mg in excess.

Time Trend in Hydroxychloroquine Prescriptions

We determined the numbers of patients who were newly started on HCQ since 2009 in 6-month intervals (Fig 3). A steady trend toward increased patient numbers is evident, starting from 15 patients in the first half of 2009 to 77 patients in the second half of 2015.

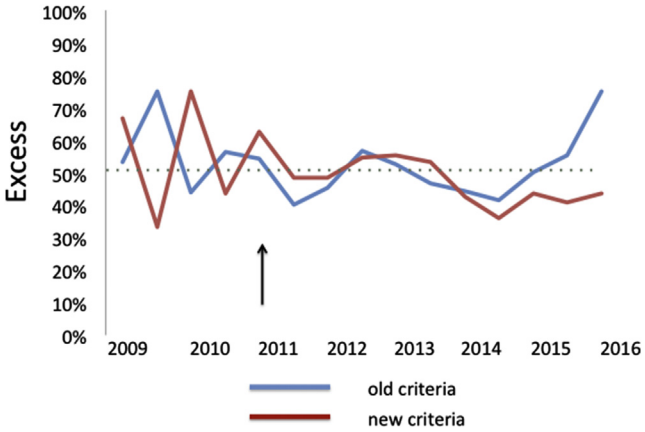

Figure 1. Time trends of hydroxychloroquine (HCQ) excess dosing. The *blue line* represents the percentage of patients receiving excess HCQ doses according to the 2011 guidelines ("old criteria"). The *red line* represents the percentage of patients on excess HCQ doses according to the revised 2016 guidelines ("new criteria"). The *arrow* marks the introduction of the 2011 dosing guidelines. The dotted line represents the 50% mark.

Discussion

The American Academy of Ophthalmology published its guidelines for HCQ retinal toxicity screening in 2011. The recommendations included specific subjective and objective tests for toxicity and information on the features of high-risk patients. High-risk features included the cumulative consumption of >1 kg HCQ, duration of treatment >5 years, increased age (with no specific cutoff), concomitant renal or liver disease, and dosing of >6.5 mg/kg/day of *ideal* body weight. These guidelines were revised in 2016, defining excess as >5.0 mg HCQ/kg of *actual* body weight/day.[7] The discussion about the optimal definition of excess HCQ dosing is ongoing. Our study does not address the merits of the different dosing algorithms. Instead, it focuses on physician adherence to the published guidelines.

The adherence to these screening guidelines has been examined in 2 prior studies. Au and colleagues[9] determined HCQ dosing and screening compliance in a retrospective analysis of 756 patients who presented to a large, multispecialty ophthalmic practice. Overall, only 46.4% of the patients received appropriate screening, 27.8% of the patients were underscreened, and 19.5% of the patients were inappropriately screened. Of note, 50.5% of patients received doses in excess of 6.5 mg/kg ideal body weight/day.

In another study, Browning[10] analyzed 219 patients who had been referred to a multispecialty ophthalmology practice for HCQ toxicity screening. Sufficient data to assess proper HCQ dosing were available in 113 of 219 patients. Potentially toxic HCQ doses were prescribed in 28 of 113 patients (24.8%), using 2011 guidelines. Of note, the ophthalmologists performing the screening

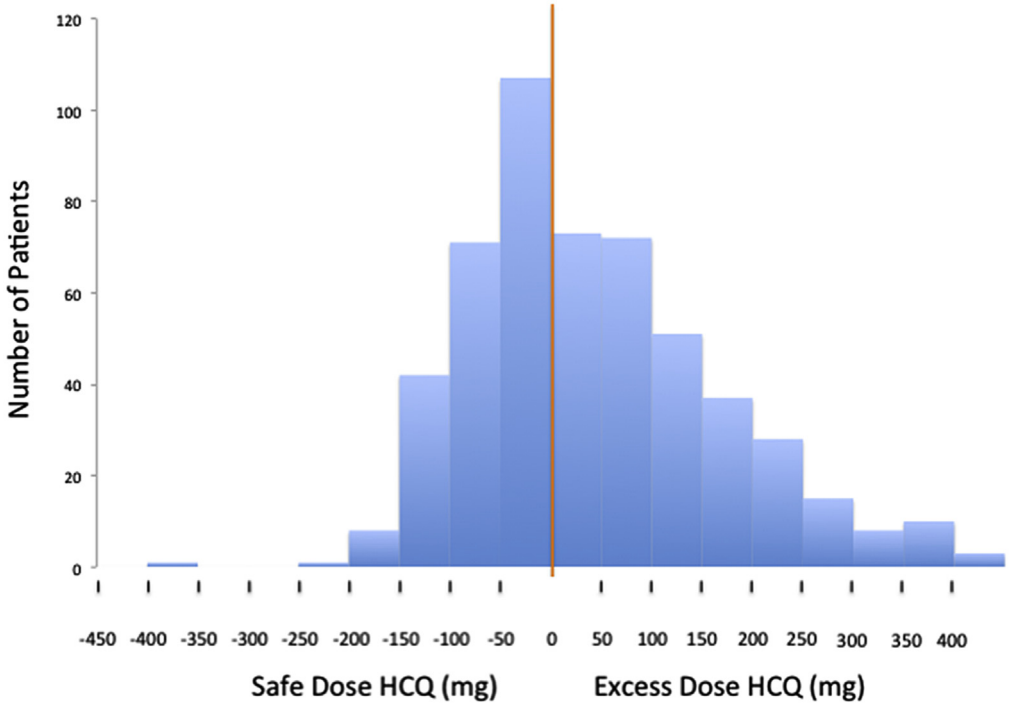

Figure 2. Hydroxychloroquine (HCQ) dosing in patients currently (August 2016) on treatment. The recommended maximum HCQ doses were calculated according to the 2016 guidelines. The histogram shows the number of patients who receive doses above ("Excess Dose HCQ") or below ("Safe Dose HCQ") the calculated safe maximum. HCQ dosing differentials were analyzed in 50-mg increments (n = 527).

evaluations failed to recommend reduction of the HCQ dose in 16 of 28 patients.

Although the 2 studies differed with regard to the calculation used to determine ideal body weight, they highlight a consistent overall trend of significant overdosing. Our study confirms and extends the key findings of the studies by Au and colleagues[9] and Browning,[10] documenting that a substantial proportion of patients are prescribed potentially toxic doses of HCQ at NorthShore University Health System. Our data may represent a low estimate because we did not analyze our patient data file for the presence of concomitant hepatic or renal disease. In addition, we did not capture the data for any patients who received their eye care outside the NorthShore health care system.

Our findings are particularly concerning given that choosing a proper starting dose is the single safest, simplest, and most cost-effective measure available. Avoiding HCQ excess dosing would potentially limit HCQ toxicity to a smaller subgroup of patients in whom toxicity might develop despite proper dosing. The continued progression of HCQ-related retinopathy after stopping the drug is a well-documented phenomenon that further underscores the importance of prevention compared with detection.[11]

One contributing factor to inaccurate HCQ dosing is the current formulation of the drug, which is available exclusively in 200-mg tablet form, limiting dosing flexibility. Potential strategies to address this issue include an expansion of the HCQ formulary options by the drug manufacturers, alternating daily dosing regimens, or the involvement of compounding pharmacies.

We suggest that the determination of the proper HCQ starting dose should not require a "screening referral" to an ophthalmologist. Instead, the creative use of the EMR to guide proper dosing would facilitate the correct choice by non-ophthalmologists, by providing electronic prompts and templates for HCQ prescribers, as suggested by Browning[10] and Parikh et al.[12] Dosing strategies based on EMRs are

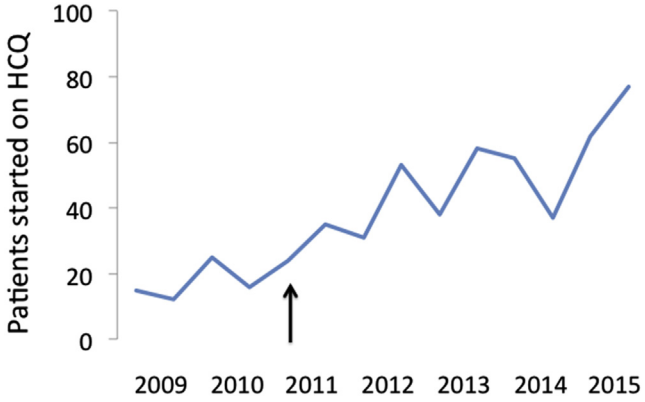

Figure 3. Time trends in hydroxychloroquine (HCQ) prescriptions. The number of patients who were newly started on HCQ since 2009 was calculated in 6-month intervals. The *arrow* marks the introduction of the 2011 dosing guidelines.

being used routinely by oncology and hematology practices.[13,14]

Our study highlights several key findings. First, it provides unequivocal evidence that a substantial percentage of patients continue to receive excess doses of HCQ, regardless of which set of guidelines are being used.

Second, it demonstrates that dosing practices did not change appreciably after the 2011 guideline revision. This may not be surprising, considering that rheumatologists would be unlikely to follow practice recommendations published in the ophthalmological literature. System-wide education and EMR-generated prompts appear to be a more promising approach to remedy this problem. We are in the process of creating such EMR-based interventions at our institution.

An analysis of the most recent dosing data at our institution demonstrates an apparently widening disparity between the percentage of patients receiving excess doses during the time period of July 2015 to June 2016 when using the formula from the 2016 guidelines compared with the 2011 guidelines (Fig 1). According to the new formula, for any given dose of HCQ, the likelihood of a "safe" dose will increase in parallel to the patient's body weight, whereas the earlier formula was solely dependent on the patient's height.

We analyzed our patients' heights and weights, and noticed a statistically significant increase in body mass index from 27.46 to 30.03 kg/m^2 between the years 2009 and 2016, respectively ($P = 0.025$). A continuation of this trend would increase the percentage of patients considered to be on "safe" doses, as defined by the updated guidelines. During the review of this article, it was pointed out that this approach would actually result in increased toxicity in some patients, and that the calculation of a safe dose should be based on lean body mass, best estimated by the lesser of actual or ideal body weight.[15] Application of this formula to our patient population would have decreased the percentage of patients receiving excess dosing from 50% to 49%, a difference that did not achieve statistical significance (data not shown).

Finally, our study shows that the overall use of HCQ continues to increase, with a 5-fold increase since 2009. This trend adds urgency to the system-wide implementation of safe dosing practices.

In summary, our study demonstrates that a significant percentage of patients within the NorthShore integrated health care system has been receiving and continues to receive HCQ in excess of the recommended doses. The published ophthalmology screening guidelines have had no appreciable impact on clinical practice, highlighting a persistent deficiency in patient care and a significant medico-legal risk. The EMR-based alerts and dosing algorithms to remedy this problem should be a high priority because they can be easily instituted and applied system-wide without creating added costs or requiring significant ophthalmology resources.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
EMR = electronic medical record; **HCQ** = hydroxychloroquine.

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