

Improving Hydroxychloroquine Dosing and Toxicity Screening at a Tertiary Care Ambulatory Center: A Quality Improvement Initiative

Sahil Koppikar¹ , Stephanie Gottheil² , Chandra Farrer¹, and Natasha Gakhal¹

ABSTRACT. **Objective.** Hydroxychloroquine (HCQ) is a commonly used weight-based medication with a risk of retinal toxicity when prescribed at doses above 5 mg/kg/day. The objectives of our study were (1) to characterize the frequency of inappropriate HCQ dosing and retinopathy screening, and (2) to improve guideline-based management by implementing quality improvement (QI) strategies.

Methods. A retrospective chart review was performed to obtain baseline analysis of HCQ dosing, weight documentation, and retinal toxicity screening to characterize current practices. The primary aim was to increase the percentage of patients appropriately dosed from 30% to 90% over a 10-month period. The secondary aim was to increase the percentage of documented retinal screening from 59% to 90%. The process measure was the number of patients with a documented weight in the chart. The balancing measure was the physician's perceived increase in time spent with each patient due to implemented interventions. QI methodology was used to implement sequential change ideas: (1) HCQ weight-based dosing charts to facilitate prescription regimens; (2) addition of scales to patient rooms to facilitate weight documentation; and (3) electronic medical record (EMR) "force function" involving weight documentation and autodosing prescription.

Results. The percentage of patients being weighed increased from 40% to 92% after 10 months. Appropriate HCQ dosing improved from 30% to 89%. Retinal screening documentation improved by 33%.

Conclusion. Dosing charts in clinic rooms, addition of weight scales, and EMR force function autodosing prescriptions significantly improved appropriate HCQ dosing practices. These interventions are generalizable and can promote safe and guideline-based care.

Key Indexing Terms: disease-modifying antirheumatic drugs, hydroxychloroquine, quality improvement, quality of care, retinal toxicity

Hydroxychloroquine (HCQ) is used widely to treat inflammatory arthritis and connective tissue disease. In rare instances, HCQ can lead to vision-threatening retinopathy. A 2014 case-control study showed that retinal toxicity is not as rare as previously thought among long-term users of the drug, with an overall prevalence of 7.5% in patients taking HCQ greater than 5 years¹. More recent publications have identified an increasing number of patients with advanced HCQ retinopathy^{2,3}. Therefore, it is important for rheumatologists, dermatologists, ophthalmologists, and primary care physicians to understand the prevalence and risk factors associated with this adverse event. In response to this, there have been several detailed publications and guidelines from the American Association of Ophthalmology and the British Society of Rheumatology focusing on the recommendations for appropriate HCQ dosing and toxicity monitoring^{4,5}.

¹S. Koppikar, MD, FRCPC, C. Farrer, PT, MSc, N. Gakhal, MD, MSc, FRCPC, Division of Rheumatology, University of Toronto, and Division of Rheumatology, Women's College Hospital; ²S. Gottheil, Division of Rheumatology, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Dr. S. Koppikar, Division of Rheumatology, Department of Medicine, Women's College Hospital, University of Toronto, Toronto, ON M5S 1B2, Canada. Email: sahil.koppikar@wchospital.ca.

Accepted for publication March 23, 2020.

The risk of toxicity is greatly dependent on daily dose, which is calculated using body weight. Traditional dosing was based on a maximum of HCQ 6.5 mg/kg of ideal body weight (IBW), rather than actual body weight (ABW), as this was considered safe for most adults to reduce the risk of retinal toxicity⁶. However, more recent evidence suggests that dosing based on ABW is more predictive of toxicity and is more accurate over a broad range of body sizes^{1,4}. Melles, *et al* suggested 5 mg/kg of ABW/day corresponded approximately to a dose of 6.5 mg/kg of IBW/day, given the average body habitus in their North American study population¹. Therefore, this change in prescribing recommendation for HCQ may be more practical in rheumatology clinics, as it has been shown that calculating doses of HCQ based on IBW is not undertaken on the majority of patients². Since HCQ retinopathy is not reversible and cellular damage may progress even after the drugs are stopped, screening guidelines were also updated to provide clarity on the diagnostic tests required from ophthalmologists and suggested more frequent monitoring schedules^{4,5}.

Despite new guidelines, there remains a lack of adherence to safe and effective dosing standards. Several North American and European studies have reported that between 37–56% of patients are still receiving doses in excess of the recommended

maximum^{7,8,9}. Gianfrancesco, *et al* have demonstrated that the percentage of individuals receiving doses in excess of guideline recommendations has decreased over time, but 30% of patients still receive doses above 5 mg/kg. Risk factors for receiving higher doses included female sex, low body weight (< 68 kg), African American race, mild liver disease, and public insurance payer¹⁰. Retinopathy screening guidelines are only being met in 82–87% of patients on average^{11,12}, with 1 center reporting screening rates as low as 49%¹³. Prior literature has identified barriers to uptake of new clinical guidelines by clinicians, including lack of awareness, lack of agreement with the evidence, external barriers, and clinical inertia^{10,14,15}. It is clear that additional steps are needed to improve guideline adherence and promote evidence-based care.

Therefore, the objective of this study was to characterize the frequency of appropriate weight-based HCQ dosing and retinal toxicity screening at an academic ambulatory care hospital in Toronto, Ontario, Canada, and to implement quality improvement (QI) strategies aimed at improving these outcomes.

MATERIALS AND METHODS

The Model for Improvement framework developed by the Institute for Healthcare Improvement was used for project development. There are 3 fundamental components: (1) developing a specific and timely aim; (2) choosing a family of outcome, process, and balancing measures; and (3) selecting interventions that focus on the underlying causes of the targeted quality gap. The interventions are then regularly refined by using Plan-Do-Study-Act (PDSA) cycles to develop and test change ideas¹⁶.

Ethics approval for this study was obtained from the Women's College Hospital Ethics Assessment Process for Quality Improvement Projects (REB # 2017-0137-E).

Baseline analysis. A retrospective chart review for baseline analysis was performed for a 3-month period, in the year prior to the study. Variables assessed were HCQ prescription dosing, patient weight documentation, retinal toxicity screening documentation, and risk factor assessment. Charts from all 4 general rheumatologists at this ambulatory hospital were reviewed from consecutive patient encounters. Charts were selected for baseline analysis if a patient was being initiated on or continuing HCQ during the clinical visit, regardless of diagnosis. A total of 70 charts, an average of 18 charts per rheumatologist, were reviewed.

The percentage of patients with appropriate HCQ dosing was determined at weekly intervals and was graphed on statistical process control (SPC) charts. Appropriate dosing was strictly defined as HCQ ≤ 5 mg/kg of ABW as documented in the chart. If a patient's weight was not documented in the electronic medical record (EMR), they were classified as "inappropriately dosed." The percentage of patients with a documented weight in the EMR and appropriate yearly retinal screening was also determined at weekly intervals and graphed on SPC charts. Demographic data, rheumatological diagnosis, and other high-risk features for HCQ toxicity were also collected.

Given the baseline results, the primary aim was to increase the percentage of patients being appropriately dosed from 30% to 90% over a 10-month period. The secondary aim was to increase the percentage of patients with documented retinal screening from 59% to 90%. A target of 90% was chosen to keep the outcome measures realistic, accounting for some error in actual practice; recognizing that rheumatologists may choose to intentionally go above the recommended guidelines in some cases; and

recognizing that patients may not get screened regardless of the efforts of their rheumatologist.

Root cause analysis. An Ishikawa diagram was created to understand root causes for inappropriate HCQ dosing and toxicity screening after speaking to relevant stakeholders, including 10 patients, 12 rheumatologists, 3 ophthalmologists/optometrists, and 5 family doctors (Figure 1). Stakeholders were interviewed after the baseline analysis and prior to the first intervention. The causes identified for inappropriate dosing and screening were (1) HCQ available only in 200-mg tablets and difficulty in quickly determining intermediate prescription doses, (2) patient and physician lack of awareness of dosing and screening guidelines, (3) weights not documented in patient charts to allow for appropriate dosing, (4) lack of time in a busy clinic to obtain weights and calculate dose, and (5) lack of government coverage for eye exams for patients < 65 years old without a ministry form.

PDSA cycles. Iterative PDSA cycles were used to refine 3 change ideas to help address the causes of inappropriate dosing and toxicity screening. Each of the change ideas was derived based on the most commonly identified barriers and feasibility of implementation within our clinics. The same 4 rheumatologists were involved with all 3 interventions, and the study did not affect any other clinicians.

- PDSA 1: HCQ dosing charts (Week 0)

To address the difficulty in quickly determining intermediate prescription doses, a user-friendly HCQ dosing chart was placed in each clinic room (Figure 2). The dosing chart helped simplify the process by providing the clinician with alternative dosing regimens between 200 mg to 400 mg based on weight.

- PDSA 2: Weight scales (Week 10)

To address the lack of weight documentation, 5 weight scales were added to clinic rooms to help facilitate the weighing of patients during clinical encounters.

- PDSA 3: EMR-based force function (Week 33)

To facilitate weight-based prescriptions, an EMR-based force function was developed to require a documentation of weight within the last 12 months in all patients being prescribed HCQ, regardless of whether it was a new or repeat prescription (Figure 3A). The EMR was also modified to provide an autodosed prescription for HCQ based on the documented weight (Figure 3B).

Family of measures. The primary outcome measure was the percentage of patients prescribed an appropriate daily dose of HCQ (based on 5 mg/kg of ABW). The secondary outcome measure was the percentage of patients with documented annual retinal screening.

The process measure was the percentage of patients with a documented weight in the EMR in the last 12 months.

The balancing measure was physician satisfaction and perceived increase in time spent with each patient due to the implemented interventions, as determined by physician survey. Physician satisfaction was assessed by means of a 5-point Likert scale asking physicians to rate each intervention for its helpfulness in appropriately prescribing HCQ and ease of integration into their usual clinic routine. Most satisfied was 5 points and least satisfied was 0 points. They were also asked to estimate the approximate increase in time spent with each patient due to the interventions.

Data analysis. Each week, 10 consecutive charts of patients prescribed HCQ were reviewed to determine weight documentation, appropriate dosing, and retinal screening. Audits were performed by 1 investigator to ensure consistency. Two months following the implementation of the forced-function intervention, an anonymous paper survey was provided to all rheumatologists to assess satisfaction and collect information related to the balancing measure. The survey process was conducted using a Likert scale and included 1 reminder.

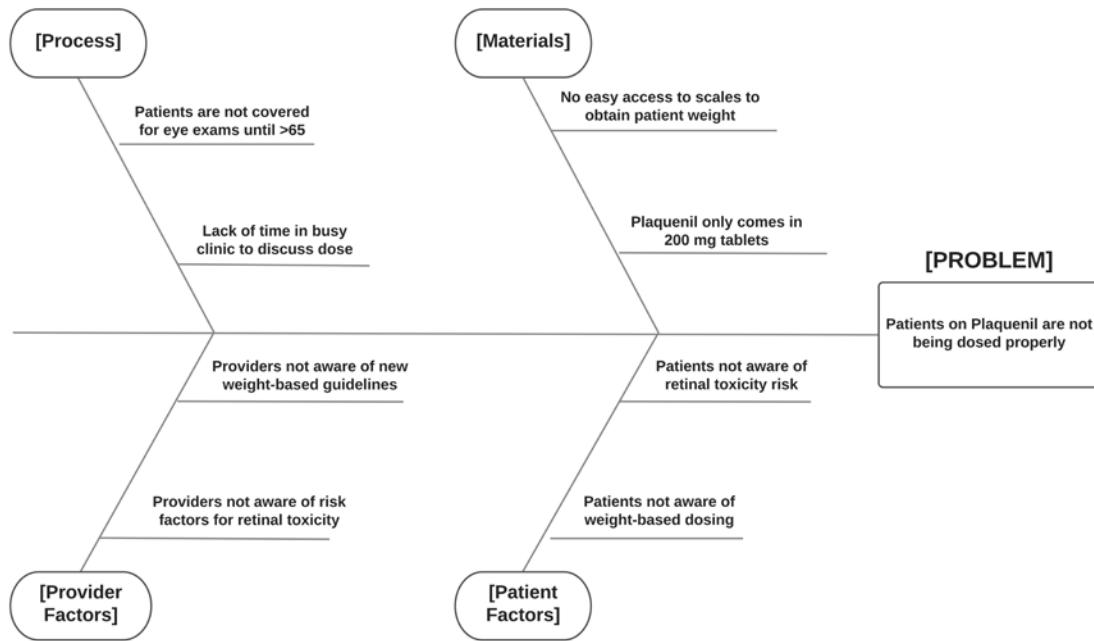


Figure 1. Ishikawa diagram showing root causes for inappropriate hydroxychloroquine dosing and toxicity screening.

Hydroxychloroquine Dosing Chart

Use the table below to determine the recommended dosing regimen for hydroxychloroquine with examples of how this could be prescribed.

NB: Dosing regimen based on 5 mg/kg of hydroxychloroquine as per 2016 AAO guidelines.

Weight	Equivalent Daily Dose	Example Dosing Regimens
80 kg or more (175 lbs or more)	400 mg	200 mg bid x 7 days
70–79 kg (154–174 lbs)	342 mg	200 mg bid x 6 days
65–69 kg (143–153 lbs)	315 mg	200 mg and 400 mg alternating days
55–64 kg (121–142 lbs)	285 mg	200 mg bid x 5 days
50–54 kg (110–120 lbs)	257 mg	200 mg daily x 5 days and 400 mg daily x 2 days
49 kg or less (109 lbs or less)	200 mg	200 mg daily x 7 days

Figure 2. Hydroxychloroquine dosing chart used in intervention 1. AAO: American Association of Ophthalmology.

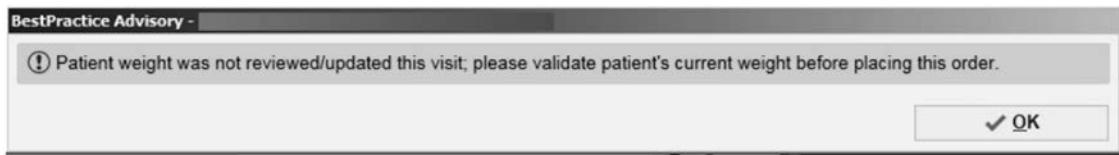
Outcomes and process measures were plotted weekly on p-type SPC charts to analyze data over time, provide feedback, and determine statistically significant ("special cause") variation.

RESULTS

Baseline analysis. During the baseline period, there were 70 unique patient charts assessed. Appropriate HCQ dosing was found in 30% of patients, while weight was documented in

40% of patients. Retinal screening was documented for 59% of patients. SPC charts did not show any special cause variation in these measures prior to implementation of the QI interventions (Figure 4, Figure 5, Figure 6).

Outcome measures. During PDSA-1, there were 92 patient charts reviewed; 230 charts were reviewed during PDSA-2; and 117 charts were reviewed during PDSA-3. The percentage



A

Name	Dose	Frequency	Disp Qt	Disp Uni	Ref	End Date	Formulary	Copay
hydroxychloroquine (PLAQUENIL) tablet - 50-54kg/110-120lbs			108	tablet	0			
hydroxychloroquine (PLAQUENIL) tablet - 55-64kg/121-142lbs	200 mg	2 times daily	120	tablet	0			
hydroxychloroquine (PLAQUENIL) tablet - 80kg/175lbs or more	200 mg	2 times daily	168	tablet	0			
hydroxychloroquine (PLAQUENIL) tablet - 49kg/109lbs or less	200 mg	2 times daily	90	tablet	0			
hydroxychloroquine (PLAQUENIL) tablet - 65-69kg/143-153lbs			132	tablet	0			
hydroxychloroquine (PLAQUENIL) tablet - 70-79kg/154-174lbs	200 mg	2 times daily	144	tablet	0			

B

Figure 3. (A) Forced function weight documentation in the EMR whenever HCQ was prescribed; and (B) autodosing prescriptions in the EMR based on patient weight. EMR: electronic medical record; HCQ: hydroxychloroquine.

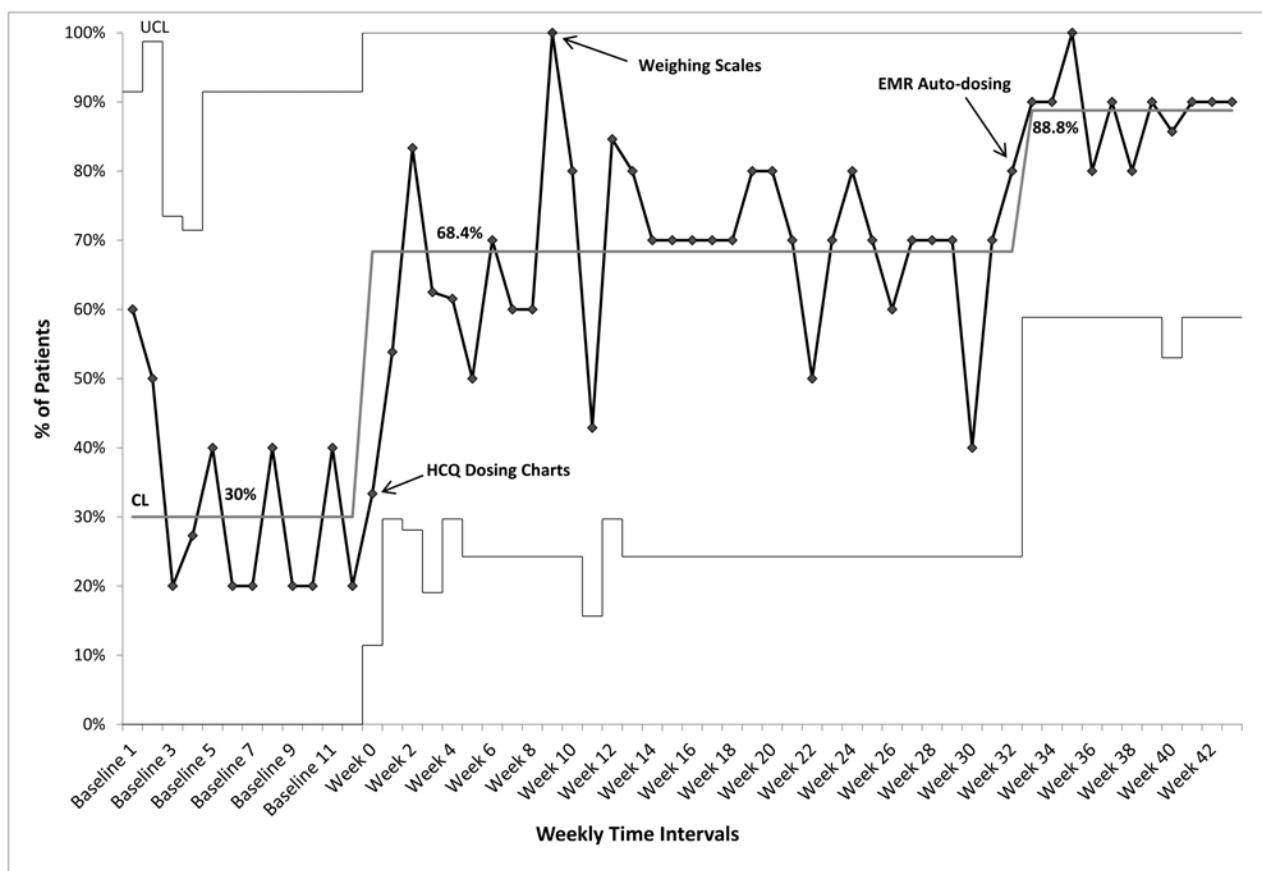


Figure 4. Percentage of patients with appropriate dosing of HCQ at baseline and over 10 months of the QI intervention. CL: center line; EMR: electronic medical record; HCQ: hydroxychloroquine; QI: quality improvement; UCL: upper control limit.

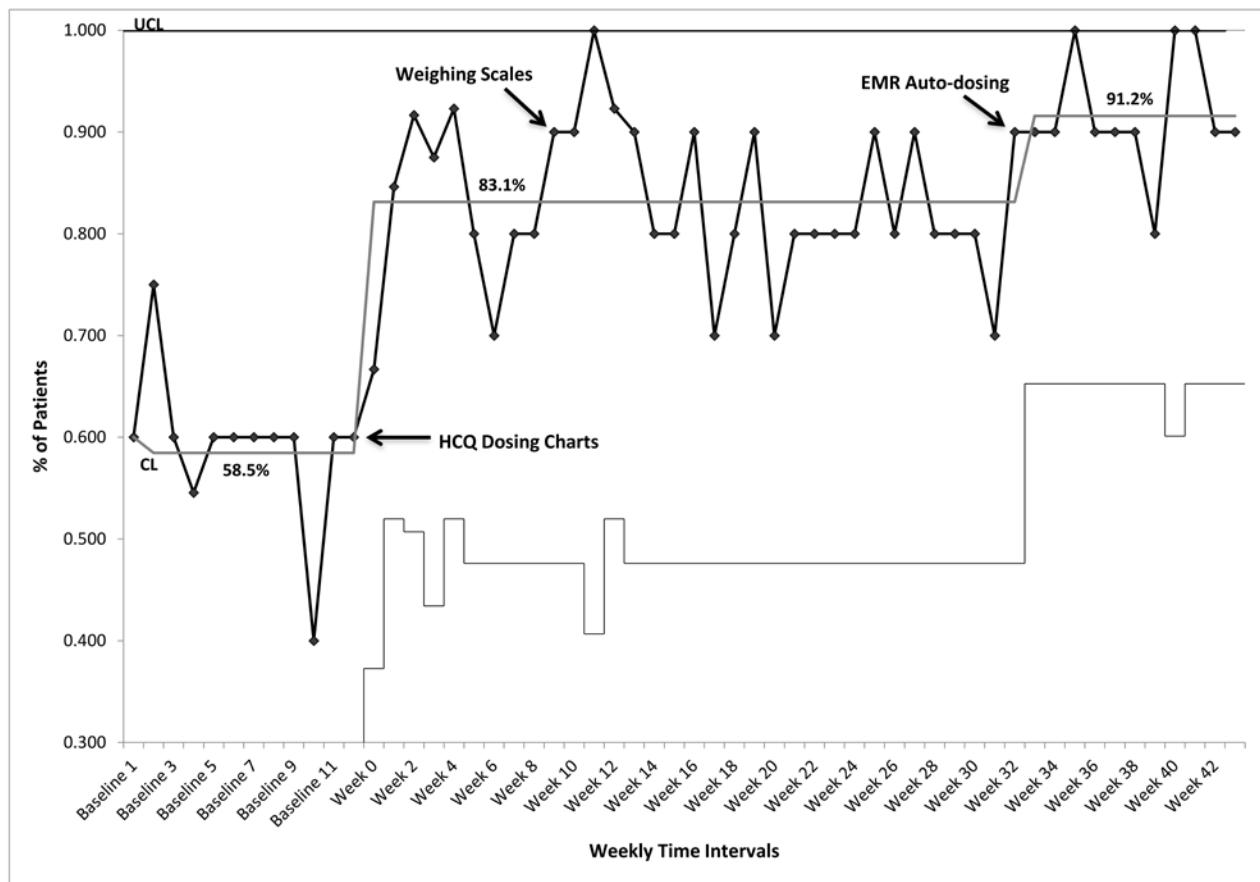


Figure 5. Percentage of patients with appropriate retinal screening documentation at baseline and over 10 months of the QI intervention. CL: center line; EMR: electronic medical record; HCQ: hydroxychloroquine; QI: quality improvement; UCL: upper control limit.

of patients being appropriately dosed on HCQ increased from 30% to 89% over the 10-month intervention period (Figure 4). There is evidence of special cause variation after the first and third interventions, as witnessed by a shift after Weeks 0 and 33, respectively. This suggests that change was not due to chance alone.

The percentage of patients with documentation of retinal screening increased from 59% to 91% over the 10-month period (Figure 5). There is evidence of special cause variation after the first intervention due to a shift.

Process measures. The percentage of patients with a documented weight over the last 12 months increased from 40% to 92% (Figure 6). There is evidence of special cause variation after both the first and third interventions.

Balancing measures. All rheumatologists rated their satisfaction and integration of the HCQ dosing charts as ≥ 4 . The average increased time spent was reported as 1 min per patient. The presence of weighing scales was viewed as less helpful, with 2 rheumatologists rating it as 3, and two rating it as 4. Weighing added on average 2 min per patient. The forced function EMR intervention was viewed favorably by all rheumatologists with a score of ≥ 4 for satisfaction and integration; it added 1.5 min on average per patient.

DISCUSSION

Guideline-based management is important to ensure safe and effective care. This study focused on improving appropriate HCQ dosing and retinal screening, given its identification as a significant issue in the field of rheumatology and ophthalmology over the last several years. A multifaceted QI intervention was noted to be effective and feasible, increasing appropriate HCQ dosing and toxicity screening to 90% at our institution over 10 months.

Based on our analysis, the introduction of the HCQ dosing charts in each clinic room significantly improved appropriate HCQ dosing by 38%. The root cause analysis suggested that the time, difficulty, and effort it took to calculate intermediate-dosing regimens was a major barrier to appropriately dosing HCQ. Therefore, the dosing chart successfully acted as a low-effort, high-yield tool assisting the rheumatologist by providing prescription regimens based on the patient's weight.

The EMR force function was also effective at significantly improving appropriate HCQ dosing. Based on the Hierarchy of Intervention Effectiveness, force functions that mandate users to complete a task in a certain way have the highest likelihood of creating desired change compared to rules, checklists, or education¹⁷. Since there was no option to bypass this EMR

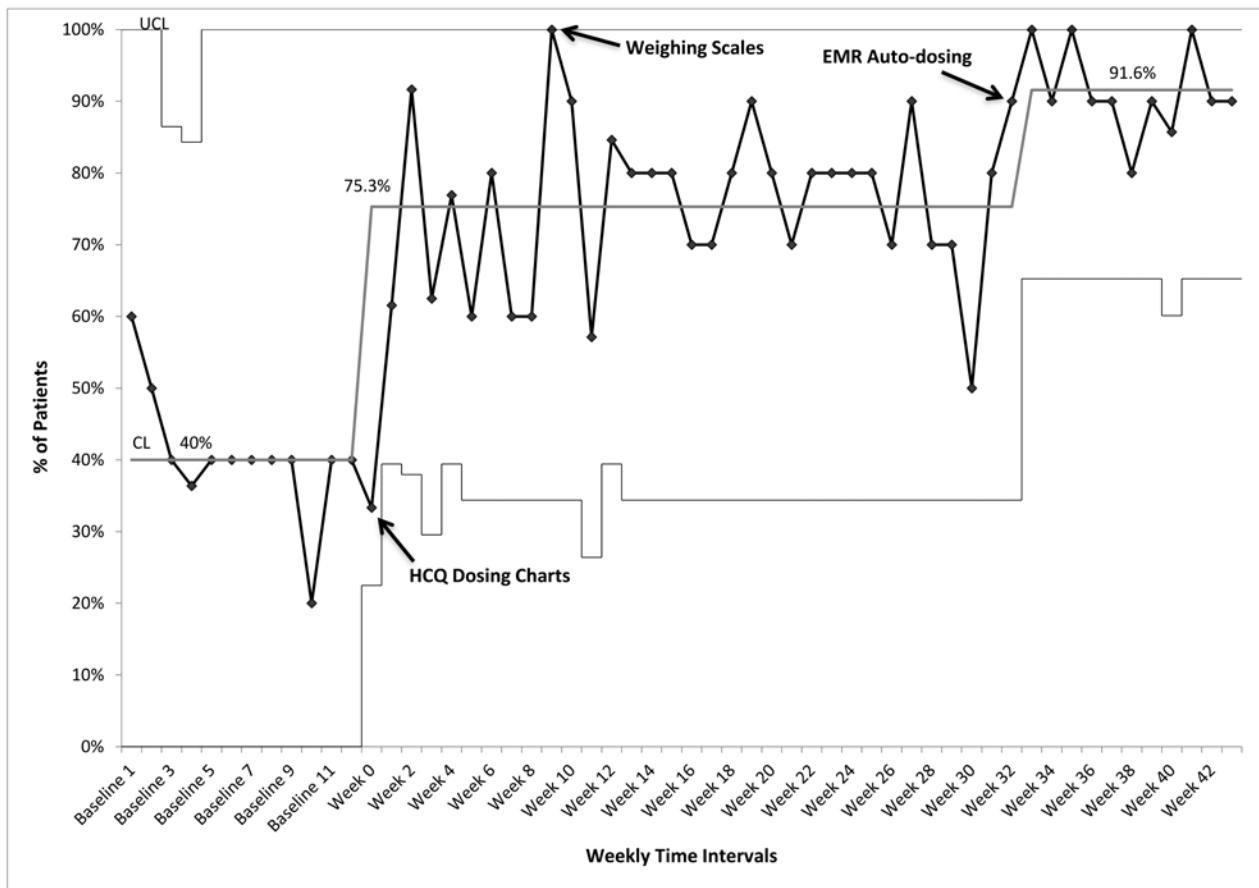


Figure 6. Percentage of patients with recorded weights in the EMR at baseline and over 10 months of the QI intervention CL: center line; EMR: electronic medical record; HCQ: hydroxychloroquine; QI: quality improvement; UCL: upper control limit.

feature, it ensured that there was a documented weight prior to prescribing HCQ. Having preset dosing regimens in the EMR, based on the HCQ dosing chart, also assisted clinicians in choosing the correct dose. However, despite the force function, 100% compliance with dosing guidelines was not achieved. This may be because the rheumatologist chose to prescribe a higher dose based on the diagnosis or clinical presentation, or that they prescribed HCQ manually without using the EMR, thereby bypassing our force function.

Although the addition of weight scales in clinic rooms did not result in any significant improvement, it may have aided in uptake by increasing stakeholder buy-in, as witnessed by sustained improvement in our SPC charts. Our second aim of improving retinal screening also had significant improvements after the first (HCQ dosing charts) and third (EMR forced function) intervention. Although there was no directed intervention targeting improving retinal screening documentation, it is likely that implementation of all change ideas served as a reminder during clinical encounters, helping to improve this outcome. Reassuringly, physician satisfaction was high following the implementation of these interventions, and there were no obvious unintended consequences to the interventions.

Our results align with previous studies that have detailed

the inappropriate dosing and toxicity screening patterns for HCQ^{7–13}. However, to our knowledge, only 1 previous study has implemented a QI strategy to improve these practices. Jessee, *et al* demonstrated that grand round lectures, modifications of EMR templates, and email reminders improved compliance with HCQ dosing from 63% to 72%. However, compliance remained poor at only 44% in patients weighing < 80 kg⁷. Our current study differed by using QI methodology, including PDSA cycles and weekly data analysis through SPC charts, as well as high-effectiveness interventions such as force functions rather than education. Unlike the Jessee, *et al* study⁷, we also examined balancing measures to ensure that the interventions were not disturbing the clinical flow.

There are a number of strengths to note in this study. Our interventions, especially the HCQ dosing chart, are simple and can be easily integrated into other rheumatology clinics to help achieve similar results. The use of SPC charts allowed data to be analyzed in real time so that further interventions could be designed and implemented. Using a survey to understand physician satisfaction helped mitigate any barriers to successful implementation of the interventions.

As with any QI study, limitations include potential confounding variables. For example, rheumatologists may have

made efforts to improve their practices after learning about our study, independent of the actual interventions. However, in our analysis, the use of process measures and statistical process charts helped to minimize the effect of confounding variables. For example, we can correlate the timing of interventions and improvement in process measures with our outcomes. In addition, we did not collect data about potential flares from HCQ dose reduction, so we cannot comment on potential flare risk by following the guidelines.

Stakeholder engagement through close collaboration with rheumatologists, trainees, administrative personnel, and EMR developers was essential in the successful implementation of the project. Determining balancing measures and mitigating issues early was of the utmost importance. We expect our results to be sustainable over time; given the simplicity of use and the fact that weight documentation is now required to prescribe HCQ, the interventions have become regular practice at our institution. The generalizability of this study allows for all interventions to be adapted for use at other clinics and hospitals, further promoting safe, guideline-based care.

ACKNOWLEDGMENT

The authors would like to thank Dr. Henry Averns for his promotion of quality improvement in rheumatology and the original idea for such a project.

REFERENCES

- Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132:1453-60.
- Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. *Eye* 2017;31:828-45.
- Latasiewicz M, Gourier H, Yusuf IH, Luqmani R, Sharma SM, Downes SM. Hydroxychloroquine retinopathy: an emerging problem. *Eye* 2017;31:972-76.
- Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123:1386-94.
- The Royal College of Ophthalmologists. Hydroxychloroquine and chloroquine retinopathy: recommendations on screening membership consultation [Internet. Accessed September 22, 2020]. Available from: www.rcophth.ac.uk/standards-publications-research/clinical-guidelines.
- Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 2011;118:415-22.
- Jessee R, Giattino S, Kapila A, et al. A quality improvement initiative to increase adherence to hydroxychloroquine dosing guidelines at an academic medical center [abstract]. *Arthritis Rheumatol* 2018;70 (Suppl 10).
- Braslow RA, Shiloach M, Macsai MS. Adherence to hydroxychloroquine dosing guidelines by rheumatologists: an electronic medical record-based study in an integrated health care system. *Ophthalmology* 2017;124:604-8.
- Jorge AM, Melles RB, Zhang Y, et al. Hydroxychloroquine prescription trends and predictors for excess dosing per recent ophthalmology guidelines. *Arthritis Res Ther* 2018;20:133-40.
- Gianfrancesco MA, Schmajuk G, Haserodt S, et al. Hydroxychloroquine dosing in immune-mediated diseases: implications for patient safety. *Rheumatol Int* 2017;37:1611-18.
- Koppikar S, Averns H. Clinical audit of hydroxychloroquine dosing and toxicity screening in patients with inflammatory arthritis and connective tissue diseases [abstract]. *Arthritis Rheumatol* 2017;69 (Suppl 10).
- Worth C, Yusuf IH, Turner B, et al. An audit of the use of hydroxychloroquine in rheumatology clinics. *Rheumatol Adv Pract* 2018;2:rky013.
- Ocon A, Shaukan SM, Mehta V, et al. Practices of hydroxychloroquine dosing based on the American Association of Ophthalmology (AAO) 2016 recommendations: A single center experience [abstract]. *Arthritis Rheumatol* 2018;70 (Suppl 10).
- Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
- Hall SF, Irish JC, Gregg RW, Groome PA, Rohland S. Adherence to and uptake of clinical practice guidelines: lessons learned from a clinical practice guideline on chemotherapy concomitant with radiotherapy in head-and-neck cancer. *Curr Oncol* 2015;22:e61-8.
- Institute for Health Care Improvement. How to Improve [Internet]. Boston, Massachusetts: Institute for Health Care Improvement. 2009. [Internet. Accessed September 23, 2020.] Available from: www.ihi.org/resources/Pages/HowtoImprove/default.aspx
- Cafazzo JA, St-Cyr O. From discovery to design: the evolution of human factors in healthcare. *Healthc Q* 2012;15:24-9.