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Original article

An audit of the use of hydroxychloroquine in rheumatology clinics

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Abstract

Objective. The aim was to audit the use, indications, complications and patient information regarding HCQ treatment in rheumatology clinics in a tertiary referral centre.

Methods. During a 9-month period, we identified all patients prescribed HCQ and attending rheumatology clinics in one hospital. We established: (i) the indication for HCQ; (ii) the prevalence of HCQ overdosing based on absolute body weight (ABW); (iii) documentation of warning of risk of retinal toxicity; (iv) systemic and ocular co-morbidities; (v) ocular symptoms during treatment; and (vi) reasons for stopping HCQ.

Results. We identified 427 patients (104 male and 323 female). The cumulative dose of HCQ was lower in RA (median 365 g; range 6–1752 g) compared with SLE (450 g; 66–1788 g) ($P = 0.105$). The median duration of HCQ therapy was 4 years (range 0.1–13 years); 28% of patients with RA and 29% with SLE continued HCQ beyond 5 years. After adjusting for ABW and renal function, 10% (31/312) had been prescribed doses exceeding recommendations. Formal documentation of counselling on ocular complications was found in only one-third of patients. Three cases of HCQ retinopathy were identified (all of whom had RA).

Conclusion. HCQ therapy is being used for >5 years in 29% of patients with rheumatic diseases, with higher than recommended doses in ~10% of patients. We recommend more rigorous scrutiny of the use of HCQ to reduce the risk of retinopathy.

Key words: hydroxychloroquine, retinal toxicity, ophthalmological screening, systemic lupus erythematosus, rheumatoid arthritis

ORIGINAL ARTICLE

Key messages

- Twenty-eight per cent (92/325) of our RA patients continue HCQ for >5 years.
- Ten per cent (31/312) of our clinic patients receive a higher than recommended dose.
- Rigorous scrutiny of HCQ dosing and duration is essential to avoid HCQ-mediated ocular toxicity.

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Introduction

The antimalarial agent HCQ is commonly used in rheumatic diseases, including RA, SLE and SS. The overall minimal prevalence of RA is estimated to be 1.16% in women and 0.44% in men in the UK [1]. The estimated prevalence of SLE in the UK is 0.1% [2]. HCQ is part of initial treatment protocols for both RA and SLE. As such, the majority of these patients would be expected

to have been prescribed HCQ at some point during their disease course.

The introduction of HCQ was not thought to be associated with the same toxicity profile as chloroquine, the use of which was known to be associated with retinal toxicity [3–6]. However, recent data suggest a prevalence of retinopathy of up to 7.5% in patients taking the drug for longer than 5 years, increasing to almost 20–50% in patients taking HCQ for ≥20 years [7, 8]. The daily dose and duration of therapy remain the most significant risk factors for the development of HCQ retinopathy [7, 8]. Traditionally, ideal body weight has been used to calculate safe dosing of HCQ. A high-quality case–control study, however, has identified the risk of retinopathy to be greatest in patients taking a daily dose of HCQ >5 mg/kg of absolute body weight (ABW), although no safe daily dose was identified [8]. ABW-based HCQ dosing has the additional advantage that it does not require patients' height measurements and is therefore easier to use in clinical practice. In line with guidelines from the Royal College of Ophthalmology, UK, we have defined a higher than recommended daily dose of HCQ as >5 mg/kg of ABW. Decisions on drug dosing and duration of HCQ therapy are usually determined by rheumatologists. However, there are few data on HCQ prescribing practice, counselling on HCQ retinal toxicity and HCQ-induced retinal toxicity in a rheumatology outpatient setting.

HCQ has been shown to have significant benefit in the treatment of SLE, and patients with SLE often respond well to HCQ monotherapy. HCQ specifically appears to be protective against renal and cardiovascular complications, which has been demonstrated to confer a survival advantage in patients with SLE [9–12]. Discontinuation of HCQ has been associated with an increased risk of disease flare in this patient group [13]. Compared with other conventional DMARDs, HCQ is generally well tolerated, and systemic adverse events are rare. It is the only DMARD that does not require regular blood test monitoring, which is a distinct advantage in certain patient groups, such as the elderly. It is also considered safe to use during conception and pregnancy [14, 15]. In RA, antimalarial agents do not exhibit a strong disease-modifying effect and have not been shown to slow radiographic progression of the disease. For this reason, they are used as monotherapy only in exceptionally mild cases of arthritis or in patients who are intolerant to other DMARDs. Here, HCQ is usually prescribed in combination with other DMARDs, such as MTX, in many first-line treatment protocols [16, 17]. HCQ is thought to support the pharmacokinetics of MTX, with higher peak and area under the curve concentrations of MTX, thereby enhancing the effect of MTX [18, 19].

We undertook an audit to evaluate the use of HCQ in rheumatology outpatient clinics to identify the indications for HCQ use, the presence of any ocular and systemic toxicity and dosing regimes. We also sought evidence of patient counselling by examining the case notes and by administering patient questionnaires to explore patients' understanding of potential HCQ-mediated retinal toxicity and recommended sight-monitoring advice.

Methods

We used a comprehensive patient registry to identify all patients receiving HCQ over a 9-month period (during 2014–15) in a single rheumatology department (Nuffield Orthopaedic Centre, Oxford, UK). The registry included details of the diagnosis and treatment indication in each patient and the details of their current drug therapy as collected at their latest clinic visit. We examined the patient record to determine indications for HCQ use, the current HCQ dose and evidence for dose adjustments. This project was registered with the Oxford University Hospitals clinical audit department. All patient sensitive data were fully anonymized after case note review. No formal ethical approval was required for this audit.

We determined whether patients were receiving a dose higher than the recommended dose based on their actual body weight. The patient record was inspected to identify documentation of counselling regarding ocular toxicity and monitoring instructions, including the standard advice to attend their opticians for annual sight tests and to alert the optometrist to their HCQ use. Patients should also have been given HCQ patient information leaflets (produced by Arthritis UK) [20]. In addition to reviewing medical records, we surveyed patients with questionaires before their clinic appointment to assess whether they had received counselling with regard to ocular monitoring and whether they had attended annual eye screening.

At treatment initiation and at the most recent clinic visit, the occurrence of ocular symptoms was established. Systemic and ocular co-morbidities were identified.

We determined the reasons for stopping HCQ during the study period, including the occurrence of HCQ retinopathy. We performed a sub-group analysis per disease using χ^2 and Student's *t*-testing where appropriate.

Results

HCQ use

We analysed the records of 427 patients receiving HCQ throughout a 9-month period. Of the 427 patients [median age 58 years (range 17–86 years)], 104 were male and 323 female, HCQ was used for RA in 76.8% (328/427), SLE in 7.5% (32/427) and other indications (e.g. SS) in 15.7% (67/427) of patients (Table 1).

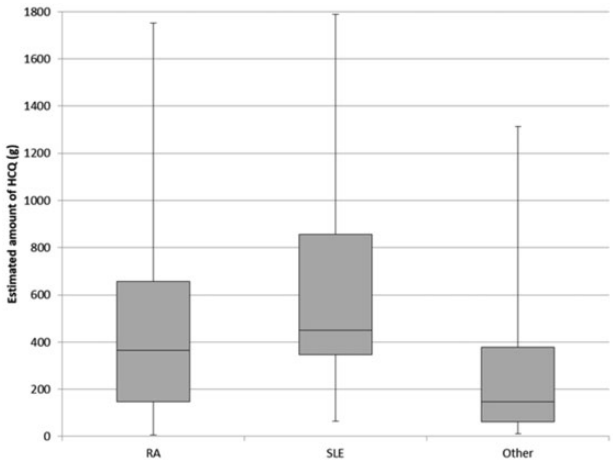
The median total dosage was lower in RA [median 365 g (range 6–1752 g)] compared with SLE [450 g (66–1788 g); $P = 0.105$; Fig. 1]. After adjustment for ABW and renal function, 10% (31/312) of patients had been prescribed more than the maximal recommended dose.

Table 1 Therapy duration and total dose exposure per disease category

Indication for HCQ	RA ($n = 328$)	SLE ($n = 32$)	Other (e.g. SS) ($n = 67$)	*P*-value
Proportion of patients	76.8% (328/427)	7.5% (32/427)	15.7% (67/427)	N/A
Median total dosage	365 g (range 6–1752 g; interquartile range 511)	450 g (66–1788 g; interquartile range 510)	146 g (12–1314 g; interquartile range 315)	$P = 0.105$ RA *vs* SLE $P = 0.0026$ RA *vs* other $P = 0.0124$ SLE *vs* other
Median therapy duration	4 years (range 1 month to 15 years)	5 years (range 1 month to 13 years)	1.8 years (range 1 month to 9 years)	$P = 0.0569$ RA *vs* SLE $P = 0.000269$ RA *vs* other $P = 0.0012$ SLE *vs* other
Therapy discontinued during observation period[a]	8.0% (26/327)	None (0/32)	7.7% (5/65)	N/A
Therapy continued beyond 5 years	28% (92/325)	29% (7/24)	15% (10/65)	$P = 0.928$ RA *vs* SLE $P = 0.0304$ RA *vs* other $P = 0.142$ SLE *vs* other

N/A: not applicable.
aWhere data were available.

Fig. 1 Cumulative HCQ dose per disease category



The median duration of therapy was 4 years (0.1–15 years), with 28% (92/325) of RA, 29% (7/24) of SLE and 15% (10/65) of patients with other diagnoses continuing beyond 5 years ($P = 0.928$ comparing RA with SLE; $P = 0$. 0.0304 and $P = 0.142$ comparing RA/SLE with other diagnoses, respectively).

Five patients reported visual deterioration; three cases were attributed to HCQ retinal toxicity (0.7%). We have reported the detailed findings in these cases separately [21]. All had macular involvement of varying severity confirmed on imaging and functional testing, and in each case HCQ had been prescribed for RA (Table 2).

Other ophthalmological findings

Twenty-two out of 427 subjects (5.2%) had ocular symptoms; the most frequent were symptoms related to ocular dryness, likely to be related to the underlying disorder. Of the patients who reported ocular symptoms, 16 patients had RA, 5 had SLE and 1 had SS.

Seventy-six out of 427 (17.8%) patients had at least one ocular co-morbidity at initiation of therapy (Fig. 2). The most common ocular co-morbidity was sicca symptoms in 9.8% (42/427) of patients. Age-related macular degeneration was present in 0.5% (2/427) of patients. Thirty per cent (128/427) of patients had concomitant diabetes mellitus and/or hypertension and/or exposure to >3 months of oral glucocorticoid therapy (Fig. 3).

Patient counselling

Counselling on ocular complications was documented in 26% (111/427) at the start of therapy and in 29% (124/427) at the most recent clinic follow-up. Among 34 patients completing a questionnaire, 64.7% (22/34) recalled verbal and 52.9% (18/34) recalled written

information regarding ocular toxicity. Twenty-seven out of 34 (79.4%) patients were aware of the need for annual ocular reviews, and 82.3% (28/34) had attended their annual eye assessment at the optometrists.

Discussion

HCQ generally has a very favourable systemic side-effect profile. However, cumulative exposure can result in ocular toxicity [7, 8]. Irreversible retinopathy may occur, especially with higher daily doses, prolonged duration of treatment and concomitant tamoxifen use or renal impairment [7, 8].

All patients identified as having HCQ retinopathy in this series had RA [21]. A recent high-quality case–control study, however, does not suggest that there is a statistically significant difference in the risk of HCQ retinopathy between different treatment indications (RA *vs* SLE *vs* other indications) [8]. We therefore cannot make any strong inferences from the fact that the three cases of HCQ toxicity identified in this audit occurred in patients taking the drug for RA, despite the generally higher doses used in SLE patients.

Recommendations for HCQ dosing vary but have included the use of doses not exceeding 6.5 mg/kg/day and using patients' ideal body weight for dose calculations [22]. More recently, the risk of HCQ retinopathy has been stratified based on dosing per kilogram of ABW [7, 8]. A dose of >5 mg/kg/day of ABW has been demonstrated to confer the greatest risk of retinopathy, and UK guidelines now suggest that those who take a dose in excess of this threshold receive annual screening [23].

There is now a consensus that the risk of HCQ retinopathy increases after 5 years of use [7, 8]. US and UK guidelines now recommend screening for retinal toxicity after 5 years of therapy for most patients. Screening should include retinal imaging with optical coherence tomography and fundus autofluorescence in addition to central, static visual field testing [7, 23]. Some patients at higher risk, such as those who concomitantly take tamoxifen, have reduced renal function (estimated glomerular filtration rate <50 ml/min/1.73 m^2), take chloroquine or take a higher than recommended dose of HCQ (>5 mg/kg/day), should begin screening after 1 year under UK guidelines [23].

In our audit, the duration of HCQ therapy exceeded 5 years in one-third of patients. Total dose exposure was greatest in SLE patients. The long-term use of HCQ in this group is not surprising given the evidence for HCQ-mediated improved survival and reduced risk of renal complications in SLE [10–12]. In addition, HCQ has been shown to stimulate nitric oxide production, reduce cardiolipin antibody production, reverse platelet

Table 2 Ocular features during treatment

Ocular features during treatment ($n = 22$)	Number of cases
Cataract	1
Sicca symptoms	6
Eye infection	1
Corneal ulcer	1
Detached retina	1
Non-specific visual symptoms/ blurred vision/deterioration in visual acuity	9
HCQ-mediated toxicity	3

Fig. 2 Ocular co-morbidity at therapy initiation

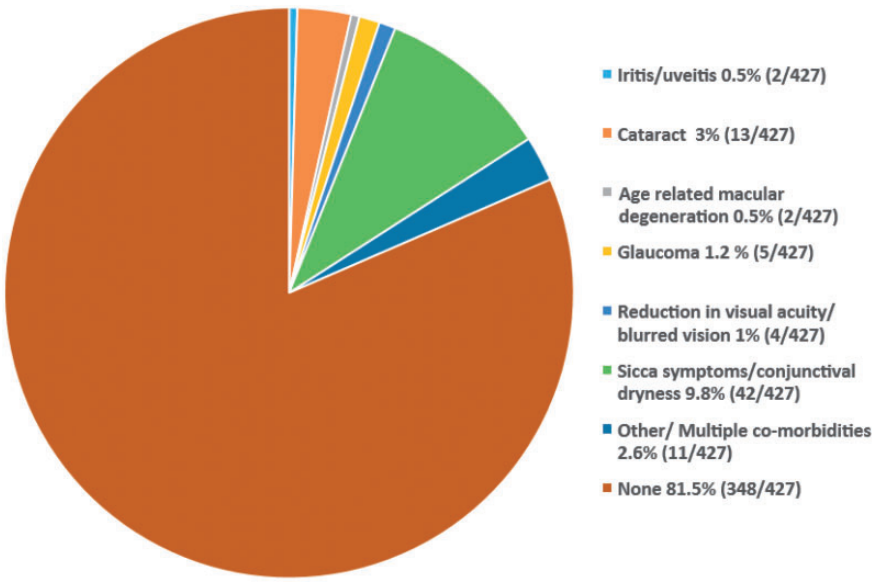
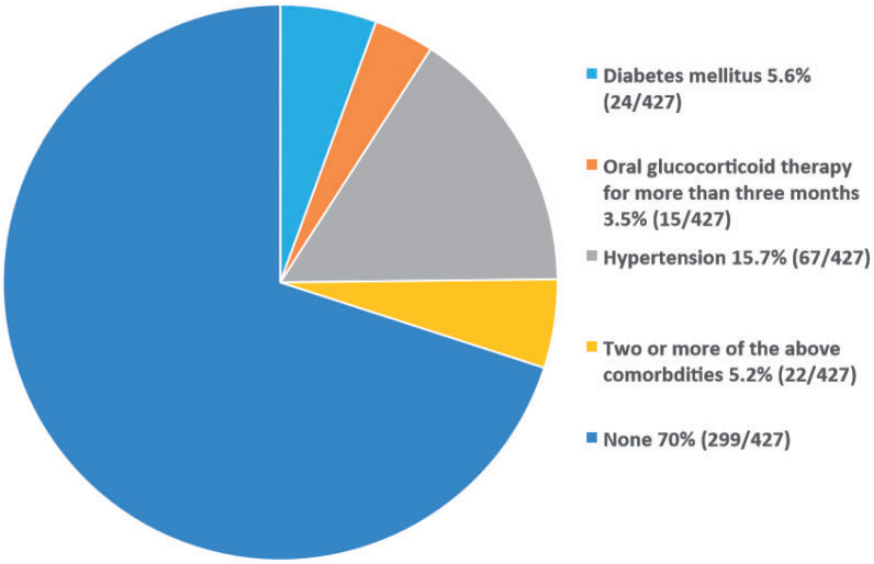


Fig. 3 Non-ocular co-morbidity at therapy initiation



activation by aPL [24–29], lower lipid profiles and reduce the risk of diabetes and thrombosis in SLE patients [30–33]. These actions confer additional survival benefits in patients already at high risk of cardiovascular disease because of their underlying rheumatological condition [34–36].

Furthermore, withdrawal of HCQ is associated with an increased risk of developing a disease flare in otherwise stable patients [13]. These data suggest that HCQ has a long-term protective effect in patients with SLE and should be considered even in the absence of overt active clinical manifestations. For this reason, HCQ is often continued in patients with SLE for many years.

In contrast to SLE, HCQ is usually used as combination therapy in RA patients and often replaced by stronger DMARDs or biologics as the disease progresses. Nevertheless, our audit suggests that as many patients with RA were taking HCQ for >5 years as were SLE patients (28 and 29%, respectively). In a recent large study of HCQ use among 10 406 SLE patients, only 17% were still fully adhering to therapy after 1 year and 47% were intermittent users [37]. In our cohort, we recorded current use, which might be influenced, in part, by treatment decisions and patient compliance. As such, we suggest that our findings are not unexpected. In patients with SS, HCQ is often prescribed for polyarthralgia. It may also improve sicca symptoms, owing to its possible effect on salivary flow attributable to inhibition of glandular cholinesterase [38].

HCQ therapy has therefore been shown to be extremely valuable in treating these rheumatological conditions. In order to continue to benefit from this drug and to minimize the risk of retinal toxicity, patients should be made aware of the potential risks of the treatment and should be informed of appropriate screening and monitoring programmes.

The number of patients who recalled having received guidance on the importance of ocular monitoring was found to be about two-thirds of cases, with 80% of patients being aware of the need for annual eye screening. Documentation of this was, however, present in only less than one-third of cases. Excellent patient information leaflets on HCQ are available in the clinic and are regularly updated by Arthritis Research UK [20]. As a result of this audit, these leaflets are displayed more prominently and given out routinely to our clinic patients once HCQ is prescribed.

It is therefore very important that rheumatologists and other regular prescribers of HCQ, such as general practitioners (GPs), are aware of the new UK guidelines produced by the Royal College of Ophthalmologists (2017) [39]. These advise on correct HCQ dosing and recommend ocular screening for patients taking HCQ for >5 years or sooner in the presence of additional risk factors, such as renal impairment or tamoxifen use [39]. Screening for HCQ retinopathy seeks to detect definitive signs of retinal toxicity on retinal imaging studies and visual field testing. A recommendation can then be made to stop the drug and reduce the risk of severe and permanent visual loss. Prescribing physicians will be responsible for referral of patients taking HCQ in whom screening is recommended.

Previous UK guidelines regarding HCQ retinopathy monitoring (2009) [40] pre-date large epidemiological studies reporting a much higher rate of toxicity than previously described [8]; and in the USA, screening for HCQ retinopathy has been advocated since 2011 [7, 41].

HCQ retinopathy is not entirely preventable, even with modern screening methods, and some patients may exhibit what is presumably an idiosyncratic response.

Patient education is therefore essential to ensure that patients understand the risk of HCQ retinopathy, the

need for a baseline examination in the eye clinic, and the HCQ screening schedule according to the Royal College of Ophthalmologists screening recommendations (2017) [39]. The initial screening visit (after 5 years of therapy for most patients) needs to be identified correctly by the prescribing physician and the patient, after which annual screening visits can be booked by the hospital eye service.

Information for patients regarding the need for this monitoring should also be made routinely available and this advice documented in the clinical record. Patients should be encouraged to report the development of any new symptoms suggesting retinal toxicity. They should also be advised to report any change of concomitant medications, such as tamoxifen, which can confer a higher risk of HCQ retinal toxicity [40].

Many rheumatology departments operate shared care agreements with GPs, who issue DMARD prescriptions. Guidance for GPs is therefore required on the appropriate duration of HCQ therapy before the decision to review treatment should be made by a rheumatologist. Additional resources and systems within rheumatology units to identify patients correctly and refer them to the hospital eye service will be required to implement these recommendations.

In summary, this audit highlights the need for a rigorous scrutiny of the use and dosage of HCQ in rheumatology clinics, with a review of medication policy, in addition to clear patient and clinician education. The implementation of a clear retinal screening and monitoring protocol should help to reduce the small but significant risk of ocular toxicity.

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