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ORIGINAL ARTICLE

Hydroxychloroquine Therapy in Sarcoidosis-Associated Uveitis

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ABSTRACT

Background/purpose: To assess the efficacy and tolerance of hydroxychloroquine in sarcoidosis-associated uveitis

Methods: Retrospective study on all patients with sarcoidosis-associated uveitis who were treated with hydroxychloroquine between 2003 and 2019 in a French university hospital.

Results: Twenty-seven patients with sarcoidosis-associated uveitis received hydroxychloroquine. The mean duration of treatment was 20.0 ± 10.9 months. At the end of the follow-up, hydroxychloroquine success was achieved in 15 (55.6%) patients. Four of them were also on oral corticosteroids, with a prednisone dose ≤5 mg/day. Under treatment, the median prednisone dose decreased from 20.0 (interquartile range (IQR), 7–25) to 5.0 (IQR, 3–6.5) mg/day ($p = .02$). The incidence rate of flare decreased from 204.6 to 63.8 per 100 person-years ($p = .02$). Hydroxychloroquine was discontinued in 12 (44.4%) patients during follow-up, including 8 (29.6%) for ineffectiveness, and three who experienced side effects.

Conclusion: Hydroxychloroquine appears as an interesting option in sarcoidosis-associated uveitis.

Abbreviations: AZA: Azathioprine; BAL: Bronchoalveolar Lavage; BCVA: Best-Corrected Visual Acuity; ENT: Ears, Nose and Throat; HCQ: Hydroxychloroquine; IOP: Intra-Ocular Pressure; IQR: interquartile range; MHC: Major Histocompatibility Complex; MMF: Mycophenolate Mofetil; MTX: Methotrexate; PMSI: Programme de Médicalisation du Système d'Information; SAU: Sarcoidosis-Associated Uveitis; SD: Standard Deviation; SUN: Standard Uveitis Nomenclature

Background

Sarcoidosis is a systemic inflammatory disease of unknown cause, characterized by the formation of non-caseating granulomas in one or more organs.[1] Any organ can be affected, most commonly the lungs and lymphatic system. Retrospective series of histologically-proven sarcoidosis indicate a high frequency of uveitis, which affects 20 to 50% of patients.[2] We, and others, have previously reported that sarcoidosis is one of the most commonly identified systemic diseases causing uveitis.[3] Uveitis generally occurs within the first year after sarcoidosis onset and can even reveal it in 30% of cases.[2] The incidence varies with age, gender, and ethnicity. All types of uveitis can occur in sarcoidosis, with a higher prevalence of anterior uveitis, which are usually granulomatous, chronic, and bilateral. Unilateral uveitis usually requires topical corticosteroids, while systemic corticosteroid therapy is usually required if topical treatment fails or is contraindicated, or in case of bilateral intermediate and/or posterior uveitis.[4,5] In 20 to 30% of patients, corticosteroids side-effects or corticosteroids dependence require the initiation of a corticosteroid-sparing treatment.[6] In 2005 the SUN working group recommended that reducing the dose of prednisone while maintaining inactive uveitis was the primary outcome for successful corticosteroid-sparing treatment.[7] Retrospective studies have shown that

various immunosuppressive agents, primarily methotrexate (MTX),[8,9] azathioprine (AZT),[9] mycophenolate mofetil (MMF),[10] and TNF-α antagonists,[11–14] are effective in this indication. However, these treatments expose patients to various side effects, including infections.

Hydroxychloroquine (HCQ) is an antimalarial drug that has been used in various dysimmune diseases for its immunomodulatory properties.[15] In sarcoidosis, its efficacy has been reported in treating various organ involvements, such as skin, joints, and lungs, as well as sarcoidosis-related hypercalcemia.[16–24] To our knowledge, the efficacy of HCQ in sarcoidosis-associated uveitis (SAU) has never been reported. In this study, we describe the efficacy and safety of HCQ in a cohort of patients with SAU.

Patients and methods

Patients

We retrospectively identified all cases of adult patients with SAU treated with HCQ seen in the ophthalmology and internal medicine departments of the Croix Rousse Hospital in Lyon, France, between December 2003 and July 2019.

Biopsy-proven sarcoidosis was defined according to the WASOG/ATS/ERS criteria.[25] In the absence of histological proof, we used Abad's modified criteria.[26] Patients had *presumed* sarcoid uveitis if they had at least two of the following four criteria: typical changes on chest X-ray or CT scan, a predominantly CD4 lymphocytosis on bronchoalveolar lavage (BAL) fluid analysis, an elevated serum angiotensin-converting enzyme (sACE) or an 18-fluorodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography. Patients had *probable* sarcoid uveitis if they had only one of the previous criteria.

Patients were included if they had been treated with HCQ for at least six months. They also had to have stopped all other immunosuppressive therapy prior to HCQ introduction. Patients with other granulomatous diseases, such as tuberculosis, were excluded.[26]

Data collection

Age, gender, and ethnicity were collected. Ethnicity was categorized by the investigators into Asian, Caucasian, African Caribbean, North African, and Sub-Saharan African. The following characteristics of the ophthalmologic examination were collected at HCQ initiation and during follow-up: biomicroscopic assessment (conjunctiva, cornea, anterior chamber, iris, lens, vitreous, and retina), intra-ocular pressure (IOP), best-corrected visual acuity (BCVA) and, optionally, optical coherence tomography (OCT), and fluorescein and/or indocyanine green angiography. Uveitis was classified according to the Standardization of Uveitis Nomenclature (SUN).[7] LogMAR BCVA was calculated from the visual acuity according to the Monoyer chart, which is widely used in France. A complete and systematic clinical examination was performed by an internist. Patients' demographics, clinical and para-clinical extra-ophthalmological characteristics of sarcoidosis, previous and/or associated treatments, including topical treatment (sub-conjunctival and periocular injection), were also recorded.

The success of HCQ was assessed by its ability to maintain inactive disease while systemic corticosteroids and/or topical corticosteroids were tapered off, defined by the following:

(1) ≤0.5+ anterior chamber cells, ≤0.5+ vitreous cells, ≤0.5 + vitreous haze, and no active retinal/choroidal lesions;
(2) ≤5 mg of oral prednisone daily and ≤2 drops of dexamethasone phosphate 0.1% (or equivalent) a day; and
(3) No discontinuation of HCQ because of adverse events.

Relapse was defined as a reactivation of ocular inflammation that necessitates a change in the therapeutic regimen (intraocular corticoid injection, increase in corticosteroid dose, or change of the corticosteroid-sparing agent).

The median dose and the number of patients requiring systemic corticosteroids were compared before HCQ initiation and at the last visit. Corticosteroid dependence was defined as failure to control ocular inflammation with >5 mg/d oral prednisone or >2 drops/d per eye of dexamethasone phosphate

0.1% (or equivalent). The occurrence of ocular complications and HCQ tolerance data were also recorded.

Statistical analysis

Categorical variables were described as numbers and percentages. Continuous variables were described by their means and standard deviations in the case of normal distribution or medians and interquartile range otherwise. Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Prednisone dose and BCVA were compared using Wilcoxon signed-ranked test given their non-normal distribution. A p value of <.05 was considered significant. Analyses were performed using version 4.1.2 of R (R Project for Statistical Computing, R Foundation).

Ethics

This study received local ethics committee approval in March 2019 (No 19–31) and was registered on clinicaltrials.gov (NCT03863782). According to French law, written consent for this study was not required due to the retrospective nature of the study.

Results

Description of the population

Among 294 patients with SAU managed at our university hospital, 29 were treated with HCQ. Among them, two were excluded because of concomitant immunosuppressive therapy. Twenty-seven patients were therefore included in this study; their characteristics at diagnosis are detailed in Table 1. The mean age of patients at HCQ initiation was 61.1 (±13.9) years. Sixteen patients (59.3%) were female and 11 (40.7%) were male. Nineteen (70.4%) patients were Caucasians, six (22.2%) were North African, and two (7.4%) were Afro-Caribbean. Sarcoidosis was histologically proven in 17 (63.0%) patients, *probable* in five (18.5%), and *presumed* in five (18.5%). Twenty-one (77.8%) patients had extraocular sarcoidosis: thoracic (n = 18, 66.7%), cutaneous (n = 4, 14.8%), joint (n = 2, 7.4%) and ear, nose, and throat (ENT) (n = 3, 11.1%). Twenty-five (92.6) patients had bilateral ocular disease. Ten (37.0%) of the patients had panuveitis, two (7.4%) had posterior uveitis, 12 (44.4%) had intermediate uveitis, and three (11.1%) had anterior uveitis. Nine patients (33.3%) had associated retinal vasculitis. Twenty-five (92.6%) patients had complications of uveitis, including cystoid macular edema (n = 21, 77.8%), glaucoma (n = 7, 25.9%), cataract (n = 12, 44.4%), and papillary edema (n = 2, 15.4%). Patients had been followed-up for their uveitis for an average of 33.9 (±32.3) months and had experienced 2.6 (±1.3) flare episodes before the introduction of HCQ, with an incidence rate of flare of 204.6 per 100 person-years of follow-up. Seventeen patients (63.0%) had received prior systemic therapy before HCQ initiation: oral corticosteroids in 17 (63.0%) patients,

Table 1. Main epidemiological and ophthalmologic features at HCQ initiation.

Number of patients	27
Mean age ± SD	61.1 ± 13.9
Sex (men/women)	11/16
Ethnic groups, n (%)	
Caucasians	19 (70.4)
North Africans	6 (22.2)
Afro Caribbeans	2 (7.4)
Sarcoidosis probability, n (%)	
Proven	17 (63.0)
Probable	5 (18.5)
Presumed	5 (18.5)
Systemic features, n (%)	21 (77.8)
Thoracic	18 (66.7)
Cutaneous	4 (14.8)
Joint	2 (7.4)
ENT	3 (11.1)
Uveitis characteristics, n (%)	
Bilateral	25 (92.6)
Chronic	27 (100)
Localization	
Anterior	3 (11.1)
Intermediate	12 (44.4)
Posterior	2 (7.4)
Panuveitis	10 (37.0)
Granulomatous	13 (48.1)
Macular edema	21 (77.8)
Papillary edema	8 (29.6)
Retinal vasculitis	9 (33.3)
Glaucoma	7 (25.9)
Cataract	12 (44.4)
Median LogMAR BCVA (IQR)	0.1 (0–0.5)
Previous treatment, n (%)	
Oral prednisone	17 (60.0)
MTX	3 (11.1)
AZA	1 (3.7)
Associated treatment at start of HCQ, n (%)	
Oral prednisone	13 (48.1)
Oral prednisone median dose in mg/d (IQR)	20 (7–25)
Intravitreal dexamethasone implant	4 (14.8)
Subconjunctival corticosteroid injection	1 (3.7)
Corticosteroids eye drops	10 (37.0)

AZA: azathioprine; BCVA: best corrected visual acuity; ENT: eye nose and throat; HCQ: hydroxychloroquine, IQR: interquartile range; MTX: methotrexate; SD: standard deviation.

methotrexate in three (11.1%) patients, and azathioprine in one (3.7%) patient.

Hydroxychloroquine therapy

Hydroxychloroquine was initiated in all patients for uveitis with oral or local corticosteroid dependence. One patient also presented with cortico-resistant parotitis.

The initial dose of HCQ was always 400 mg/d and was not modified during follow-up. At the time of HCQ initiation, 13 (48.1%) patients were also treated with oral corticosteroids at a median dose of 20 (interquartile range (IQR), 7–25) mg/day, four patients were treated with an intravitreal dexamethasone implant, one patient was treated with a subconjunctival corticosteroid injection, and 10 patients were treated with >2 corticosteroids eye drops. Patients were treated with HCQ for a mean duration of 20.0 ± 10.9 months and the average total follow-up time was 53.9 ± 32.7 months. Fourteen (51.9%) patients had a relapse under HCQ with a total of 23 relapses. The median time to first relapse after the beginning of HCQ was 34.8 (IQR, 19.0–66.0) weeks, and the incidence rate of flare decreased to 63.8 per 100 person-years of follow-up ($p = .02$). These flares

required subconjunctival corticosteroids injections in two patients and dexamethasone intravitreal implants in five patients. One patient required oral corticosteroid initiation, and MTX was finally introduced to two patients due to the inability of HCQ to control ocular inflammation. Two other patients who had not relapsed were also treated with intravitreal dexamethasone implants to control macular edema. Best corrected visual acuity evolution could be analyzed in 18 patients (36 eyes). Among them, BCVA deteriorated in 11 eyes, improved in five eyes, and stabilized in 20 eyes, including 16 eyes that have maintained perfect BCVA (LogMAR visual acuity = 0). The median best-corrected logMAR VA was improved in the 36 eyes from 0.1 (IQR, 0–0.5) to 0 (IQR 0–0.3), though this change was not statistically significant ($p = .32$).

At the end of the follow-up, HCQ success was achieved in 15 (55.6%) patients (Figure 1). Among them, four patients (all initially treated with oral corticosteroids) were still treated with oral corticosteroids, with a dose of prednisone ≤ 5 [range 4–5] mg/d, and no patient was receiving corticosteroid eye drops. Among all patients, the median prednisone dose decreased to 5 (IQR, 3–6.5) mg/d under treatment ($p = .02$). Hydroxychloroquine was discontinued in 12 (44.4%) patients during follow-up, including eight (29.6%) for ineffectiveness. Four patients experienced adverse events on HCQ with non-severe digestive disorders in two patients, induced hyperpigmentation in one patient, and asymptomatic retinopathy attributed to HCQ in one patient. Three of these patients discontinued HCQ due to these side effects. Hydroxychloroquine was also discontinued in one patient due to severe uveitis-related maculopathy preventing HCQ-retinopathy screening by automated visual-field and spectral-domain optical coherence tomography.

Results according to the anatomical class of uveitis show that the HCQ success was achieved in 66.7% of patients with anterior uveitis or intermediate uveitis, compared with only 41.7% of those with posterior uveitis or panuveitis (Table 2).

Discussion

Our study demonstrated the value of HCQ in the treatment of SAU. The introduction of HCQ resulted in a statistically significant decrease in the median corticosteroid dose as well as in the uveitis incidence rate of flare. Patients' visual acuity was improved, although this was not statistically significant. We observed good tolerance of HCQ, with only one case of antimalarial-induced maculopathy.

We found no case reports/series evaluating the efficacy of HCQ in ocular sarcoidosis. Clinicians are probably reluctant to introduce HCQ for ophthalmological diseases because they fear antimalarial-induced maculopathy. Although chloroquine (CQ) and HCQ were originally used for the treatment of malaria, they are now widely used for their immunomodulatory properties. Their major mechanism of action is based on their interference with antigen presentation to CD4 T-cells which is one of the first steps in granuloma formation. Indeed, CQ/HCQ inhibit antigen digestion by raising lysosome pH and interfering with antigenic peptide loading onto class II MHC.[27,28] Some studies also indicate that they reduce pro-inflammatory interleukins,[29,30] inhibit endosomal toll-like
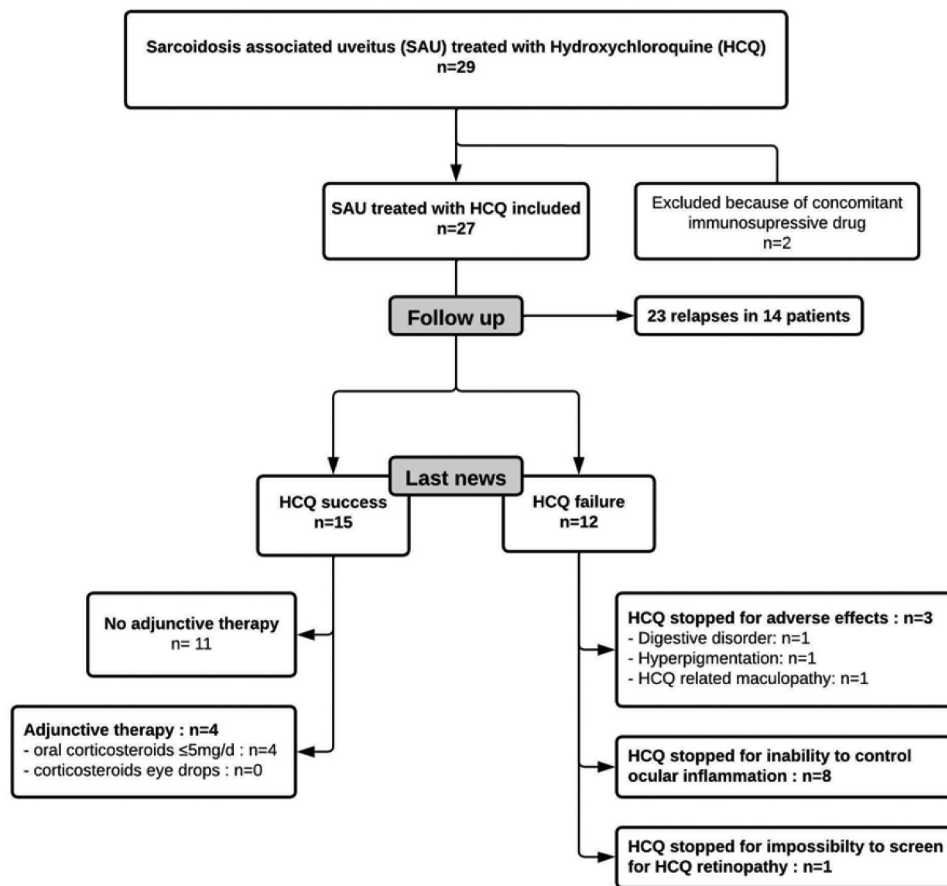
Figure 1. Flow chart. HCQ: hydroxychloroquine; SAU: sarcoidosis associated uveitis.

Table 2. HCQ outcomes by anatomical class of uveitis.

	Total population (n = 27)	AU (n = 3)	IU (n = 12)	PU (n = 12)
HCQ success, n (%)	15 (55.6)	2 (66.7)	8 (66.7)	5 (41.7)
No adjunctive therapy	11 (40.7)	1 (33.3)	8 (66.7)	3 (25.0)
Oral corticosteroids ≤5 mg/d	4 (14.8)	1 (33.3)	0	2 (16.7)
HCQ failure, n (%)	12 (44.4)	1 (33.3)	4 (33.3)	7/12 (58.3)
HCQ stopped for inefficacity	8 (29.6)	1 (33.3)	2 (16.7)	6 (50.0)
HCQ stopped for adverse effect	3 (11.1)	0	2 (16.7)	0
HCQ stopped for impossibility to screen for HCQ retinopathy	1 (3.7)	0	0	1 (8.3)
Incidence rate of flare, before vs on HCQ (100 p/y)	204.6 vs 63.6	300.2 vs 16.7	207.7 vs 51.1	177.7 vs 87.7

AU: anterior uveitis; HCQ: Hydroxychloroquine; IU: intermediate uveitis; PU: posterior uveitis and panuveitis; p/y: person-years.

receptors, and have anti-inflammatory effects by inhibiting prostaglandin synthesis or lipid peroxidation.[31,32] Nowadays, HCQ is preferred over CQ because of a better safety profile.[27] Chloroquine has been used in sarcoidosis as a steroid-sparing agent for decades, since Siltzbach reported its efficacy in patients with skin and intrathoracic involvement in 1964.[33] Its efficacy has been demonstrated in pulmonary sarcoidosis in two small randomized trials and one more recent retrospective cohort study.[21,23,34] Hydroxychloroquine efficacy has been demonstrated in small case series of cutaneous,[16,35] neurological,[36] and bone[37] sarcoidosis, and is also suggested in some case reports of various other extra-thoracic involvements.[38–41] Despite the lack of evidence for HCQ efficacy in the literature, HCQ is routinely used by physicians, mostly for skin

and joint involvements, as well as some non-severe forms of sarcoidosis, including eye involvement.

There was a large proportion of anterior and intermediate uveitis in our study (n = 15, 45.5%) while the use of a steroid-sparing treatment is not recommended in first line therapy in the recently published guidelines.[42] Furthermore, 47% of patients had not received oral corticosteroids/systemic therapies prior to the introduction of HCQ. This supports an over-representation of non-severe uveitis in our study. The choice of HCQ in these less severe uveitis cases may have been justified by the lack of efficacy data in the literature, and by the better tolerance profile of immunosuppressive treatments.

Our study found mixed results on the efficacy of HCQ in SAU. Only 15/27 (55.6%) patients had quiet uveitis on

HCQ at the end of follow-up without the need for additional immunosuppressive therapy. However, subgroup analysis according to the anatomical class of uveitis shows greater efficacy in anterior and intermediate uveitis, as opposed to posterior uveitis. The use of HCQ could therefore be of interest in anterior and intermediate uveitis that are generally not vision-threatening, to avoid the use of immunosuppressive and biologic drugs. Clinical trials evaluating the efficacy of HCQ in pulmonary sarcoidosis and extra-pulmonary sarcoidosis will start soon. These trials may show that patients with extraocular sarcoidosis develop less ocular sarcoidosis on HCQ.

Nevertheless, a significant finding of our study is that HCQ appears to have an interesting steroid-sparing effect, with a significant decrease in corticosteroid dose over the study period. At last visit, no patient was treated with >5 mg/day of prednisone among those still on HCQ. There is a consensus that maintaining inactive uveitis while reducing the dose of prednisone to 7–10 mg/d or less should be the primary goal for a successful steroid-sparing agent.[4,5,7] Additionally, our study suggests that HCQ reduces the incidence of ocular relapses with an incidence rate of flare that went from 204.6 to 63.8 per 100 person-years of follow-up after HCQ initiation and preserves vision.

We report a relatively good tolerance of HCQ in our study, with only three patients who discontinued HCQ because of adverse events. Reassuringly, only one patient showed early signs of antimalarial-induced retinopathy, which required HCQ discontinuation before any visual acuity impairment. However, the risk of retinal toxicity is dependent on the daily dose and duration of use. At recommended doses (≤6.5 mg/kg/d), the risk of toxicity up to 5 years is under 1% while the average follow-up with HCQ in our study was < 2 years, which is usually too early to detect the initial stages of this retinopathy.[43] It is therefore probable that other cases of HCQ retinopathy could develop among enrolled patients during longer follow-up. Regular screening with multimodal imaging is necessary to detect the initial stages of retinopathy to improve the visual prognosis of these patients.[44,45] There are no specific data to suggest that patients with uveitis are at higher risk, but macular edema may cause test abnormalities that interfere with the interpretation of screening procedures.[46]

Our study has several limitations. First, the retrospective nature of our study has resulted in substantial missing data, especially regarding ophthalmological examination details, and the small sample size implies that our results should be interpreted with caution. Moreover, many patients have received additional treatment, most notably dexamethasone intravitreal implants. This may have resulted in an overestimation of the efficacy of HCQ as a cortisone-sparing drug. Furthermore, we used the Abad's modified criteria to include patients and not the diagnostic criteria for SAU that were recently published by the SUN working group in 2021.[26,47] Nevertheless, there are many similarities between these criteria, and we have verified retrospectively that our patients meet the SUN criteria for proven, probable or suspected sarcoidosis. Finally, the absence of a control group is a limitation. The positive results therefore encourage a larger prospective controlled study.

Conclusion

Hydroxychloroquine is an interesting therapeutic option in SAU because of its steroid-sparing effect, its ability to prevent relapse and preserve vision, as well as its excellent tolerance. Its effectiveness seems to be more important in anterior and intermediate uveitis. However, these results cannot be extended to the most severe uveitis and should be confirmed by larger prospective studies. There was no apparent increase in antimalarial-induced retinopathy, but the feasibility of appropriate ophthalmologic monitoring in case of macular edema should be verified.

Authors' contributions

AB collected the data. AB and PS contributed equally to the redaction of the manuscript. Data analysis was made by AB and TEJ. MF and PS take responsibility for the integrity and accuracy of the data. AB, PS and LK participated in the clinical management of the patients enrolled in the study. All authors revised the manuscript. All authors have read and approved the final manuscript.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent for publication

According to French law, written consent for this study was not required due to the retrospective nature of the study.

Ethics approval and consent to participate

This study received local ethics committee approval in March 2019 (No 19-31) and was registered on clinicaltrials.gov (NCT03863782).

Disclosure statement

No potential conflict of interest was reported by the authors.

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