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Hydroxychloroquine monotherapy in sarcoidosis: Indications, efficacy, and side effects

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Abstract. *Background and aim:* In sarcoidosis that is not threatening vital internal organs such as the heart, central nervous system or lungs, immunomodulatory treatment, such as hydroxychloroquine can be considered. Despite its common use, limited data are available regarding effectiveness and side effects as monotherapy in sarcoidosis. Recommendations on its usage are based on expert opinion as literature is scarce. *Methods:* This retrospective study examines real-world data about the indications, effectivity and side effects of hydroxychloroquine monotherapy in sarcoidosis patients with no damage to the vital internal organs. Successful treatment was defined as continuation after 24 weeks without step up therapy or worsening of symptoms. *Results:* Sixty patients were eligible for the study. Starting dose was 400mg/day, lowered to 200mg/day after 3 months in most patients. The predominant treatment indications were musculoskeletal 45 (75%) and cutaneous involvement 13 (22%). Thirty-three patients (55%) continued treatment after 24 weeks. Twenty-four patients (40%) mentioned side effects, mainly gastrointestinal, leading to treatment discontinuation in eleven patients (18%). No severe side effects were seen. Continuation after 24 weeks was significantly higher in patients with cutaneous involvement compared to other indications 85% vs 47% respectively (p =0.02). *Conclusions:* Treatment with hydroxychloroquine monotherapy was satisfactory in 55% of patients, especially for cutaneous involvement. However, it poses considerable non-severe side-effects.

Key words: sarcoïdosis, monotherapy, hydroxychloroquine

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause with different clinical manifestations, often related to the organs affected. Some symptoms, however, are not organ-specific and include fatigue, cognitive impairment and pain which can have a negative impact on quality of life (1). Pharmacological treatment of sarcoidosis can be initiated to either prevent further specific organ damage or alleviate symptoms and includes corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) or anti-tumor necrosis factor alpha (anti-TNF-α) inhibitors. However, these treatment options can cause serious side effects that negatively affects the patient's quality of life (2). Especially in sarcoidosis which is not threatening vital internal organs such as heart, central nervous system, lungs or non-organ-specific manifestations, immunomodulatory treatment such as hydroxychloroquine (HCQ) might be favoured (3–6). Recently, a guideline on the management of sarcoidosis has been published including the oral antimalarial drug, hydroxychloroquine (3,4). Recommendations on the use of HCQ are based on current clinical practices as literature

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is scarce and limited to some cases for cutaneous (7–10) and musculoskeletal involvement (11–13) Although the underlying mechanism in sarcoidosis is still largely unknown, it is suggested that HCQ suppresses inflammation (6,12) with potentially fewer side effects (14).

This study aimed to investigate the main treatment indications, satisfactory treatment and side effects of HCQ monotherapy in patients with sarcoidosis.

Method

Study design

This is an observational retrospective database analysis evaluating the effectivity of HCQ monotherapy in sarcoidosis patients for 24 weeks at the ILD Center of Excellence, member of European Reference Network-Lung, St Antonius Hospital, Nieuwegein, the Netherlands.

Subjects, data source and data extracted

Between 2008 and 2022, data from consecutive sarcoidosis patients, who gave written informed consent, were extracted from the BIOBANK ILD and managed using the REDCap electronic data capture tool hosted at the St. Antonius Hospital. The study was approved by the local ethics committee (MEC-U) under study number R05-08A. The diagnosis of sarcoidosis was established according to the current guideline (15). For this study, the selection of patients is based on a query (sarcoidosis', 'plaquenil' or 'HCQ' or 'hydroxychloroquine' and 'biobank informed consent')) from the electronic health record system (*Epic Hyperspace 2021*) (Figure 1). The inclusion criteria were:

- The indication for HCQ therapy was sarcoidosis;
- Monotherapy HCQ, no other medication for sarcoidosis;
- Follow-up for at least 24 weeks (disregarding continuation/discontinuation of HCQ).

For patient-reported effectiveness, electronic health records were screened. Extracted were demographical, clinical and anamnestic data from the initiation of HCQ treatment until 24 weeks. Treatment continuation was determined based on a shared decision by the patient and treating physician. When they both agreed that the therapy did have an effect and there were no significant side effects, the patient continued after 24 weeks. In the absence of an exact endpoint, we used the continuation of therapy without escalation to immunosuppressive therapy or worsening of symptoms at 24 weeks as a surrogate endpoint for satisfactory treatment.

Furthermore, a chart review was conducted to evaluate the individual anamnestic response to treatment. Because of the retrospective nature of this study and the missing systematic evaluation, the anamnestic response could not be classified further. Additionally, we focussed on side effects, especially those that caused discontinuation of therapy and looked specifically at retinal toxicity and QT prolongation in electrocardiograms (ECG).

Statistical analysis

Among all patients, descriptive statistics were calculated and reported as absolute numbers or percentages. When values were normally distributed (Kolmogorov and Shapiro > 0.05) the mean (standard deviation [SD]) and for comparison between two paired groups the paired T-test was used. When the values were not normally distributed (Kolmogorov and Shapiro < 0.05) the median (interquartile range [IQR]) and for comparison between two paired groups the Wilcoxon Rank test was used. To compare two categorical binary unpaired groups a chi-square test was used. Statistical significance was considered when a p-value was smaller than 0.05 (2-sided).

Results

Baseline characteristics

The pre-defined query from the electronic health record system revealed 169 potentially relevant patients, of which 60 were eventually included in the study because they used monotherapy HCQ for sarcoidosis for at least 24 weeks (Figure 1).

In the baseline table, the demographics and clinical characteristics are displayed (Table 1). The median time in years between diagnosis and the start of HCQ treatment was 3 years. The predominant indication for HCQ was musculoskeletal pain (45 patients; 75%), followed by cutaneous sarcoidosis

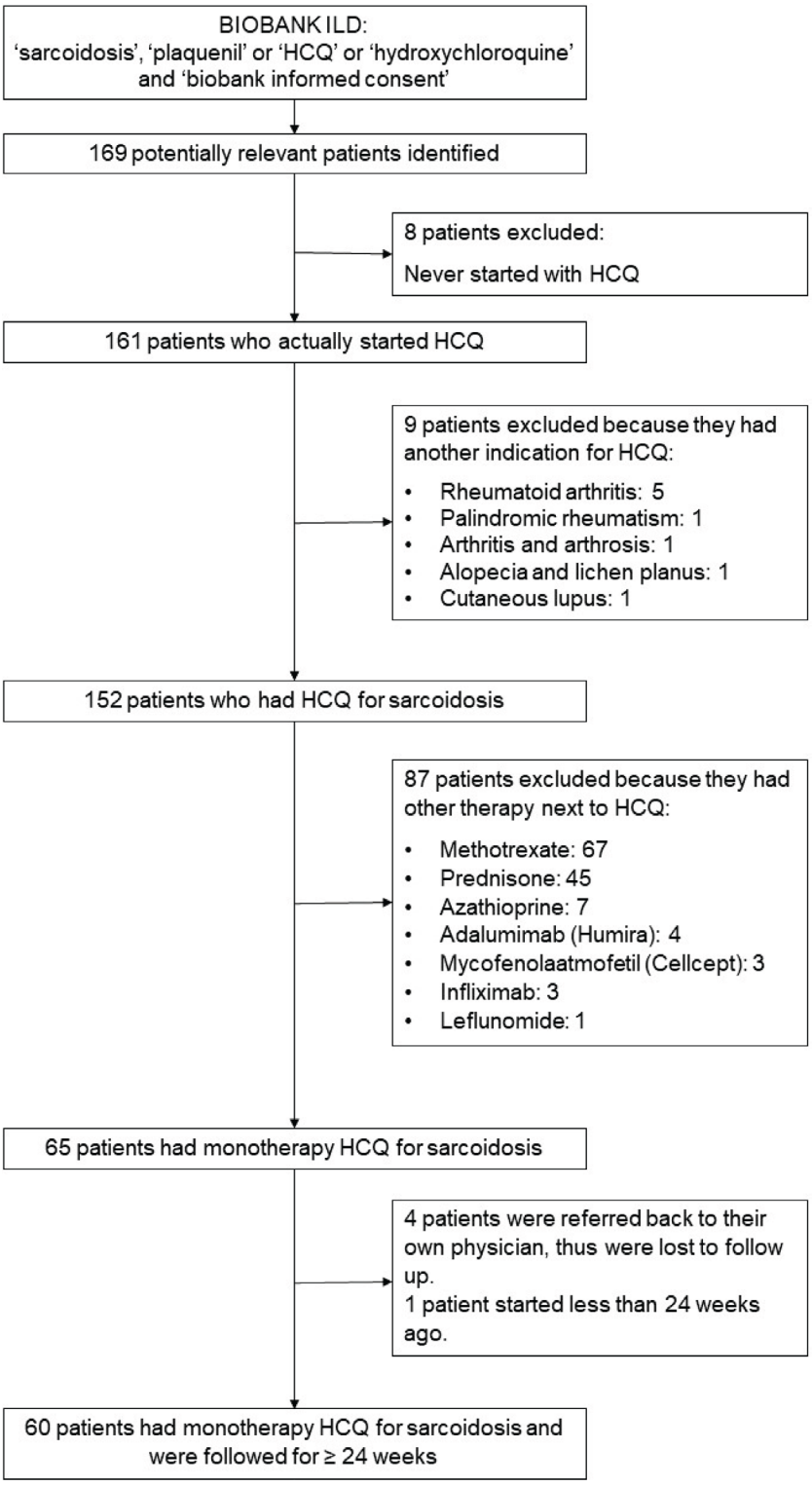

Figure 1. Flowchart study inclusion. Abbreviations: ILD: Interstitial Lung Disease; HCQ: Hydroxychloroquine.

Table 1. Baseline characteristics

Baseline characteristics	
Total number of patients	**60**
Age at start HCQ (mean, SD)	48 ± 11
Time in years between diagnosis and start HCQ (median, IQR)	3 (1-7)
Male sex (N, %)	32 (51)
Caucasian (N, %)	51 (81)
Diagnosis	
Pathological proven (N, %)	43 (72)
Broncho alveolar lavage (BAL) diagnosis (N, %)	4 (7)
Clinical multidisciplinary team diagnosis (N, %)	8 (13)
Löfgren syndrome diagnosis	5 (8)
Indication HCQ (≥1 indication is possible)	
Musculoskeletal pain (N, %)	45 (75)
Cutaneous manifestation (N, %)	13 (22)
Fatigue (N, %)	6 (10)
Pulmonary symptoms (N, %)	6 (10)
Other (N, %)	4 (7)
Starting dosage HCQ	
200 mg per day (N, %)	3 (5)
400 mg per day (N, %)	57 (95)

Abbreviations: HCQ: Hydroxychloroquine; SD: standard deviation; IQR: interquartile range; N: number.

(13 patients; 22%). Most patients (57; 95%) started with 400mg/day and reduced this to 200 mg/day after three months.

Treatment response

Of all 60 patients who started monotherapy HCQ, 33 patients (55%) continued HCQ treatment after 24 weeks (Figure 2). Within this group of patients still on treatment, 19 patients (58%) reported anamnestic improvement of symptoms or cutaneous lesions, while for the other 14 patients (42%), the anamnestic response was moderate or not sufficiently noted.

For the group that discontinued within 24 weeks (27 patients; 45%), the reason for discontinuation of HCQ treatment was foremostly a combination of ineffectiveness and side effects. The predominant reason for discontinuation was noted (Figure 2).

Differentiating between patients with cutaneous manifestations as the main treatment indication (with or without musculoskeletal symptoms) and the other patients (non-cutaneous, predominantly musculoskeletal pain) resulted into a significant difference. Respectively 11 out of 13 (85%) of the cutaneous group and 22 out of 47 (47%) of the non-cutaneous group continued with HCQ therapy after 24 weeks (p =0.02) (Figure 2).

Prevalence of potential side effects

A total of 24 patients (40%) mentioned possible side effects (table 2). The majority of the side effects were mild, but led to discontinuation of HCQ treatment in 11 patients (18%). Most patients mentioned more than one side effect, therefore the accumulated number is larger than the total number of patients. The predominant side effect was gastrointestinal related (10 patients; 17%) including but not limited to nausea (5 patients; 8%) (table 2). No cardiac events, such as arrhythmias, were observed in any patients. 12 patients (20%) underwent an ECG, none showed QT prolongation, except for one patient with other cardiac comorbidities.

Ocular toxicity

In our cohort, 50 patients (83%) were screened by an ophthalmologist before starting HCQ, none had a contra-indication for HCQ initiation. The recommendation of The Royal College of Ophthalmologists states that when a patient uses hydroxychloroquine for more than 5 years an annual screening is indicated (16). 27 of the 60 participants (45%) were screened while using HCQ. Among 27 patients, 17 were assessed by an ophthalmologist for non-HCQ-related eye symptoms before reaching the 5-year HCQ mark. Since most participants did not use HCQ for more than 5 years, most were not screened, but all patients were instructed to report any vision impairment.

Of the 10 patients using HCQ for over 5 years and screened via visual field testing, none showed macular toxicity and retinopathy caused by HCQ.

Discussion

This study reports the main treatment indications, efficacy and side effects of HCQ monotherapy in patients with sarcoidosis. The main indications for HCQ treatment were musculoskeletal pain and

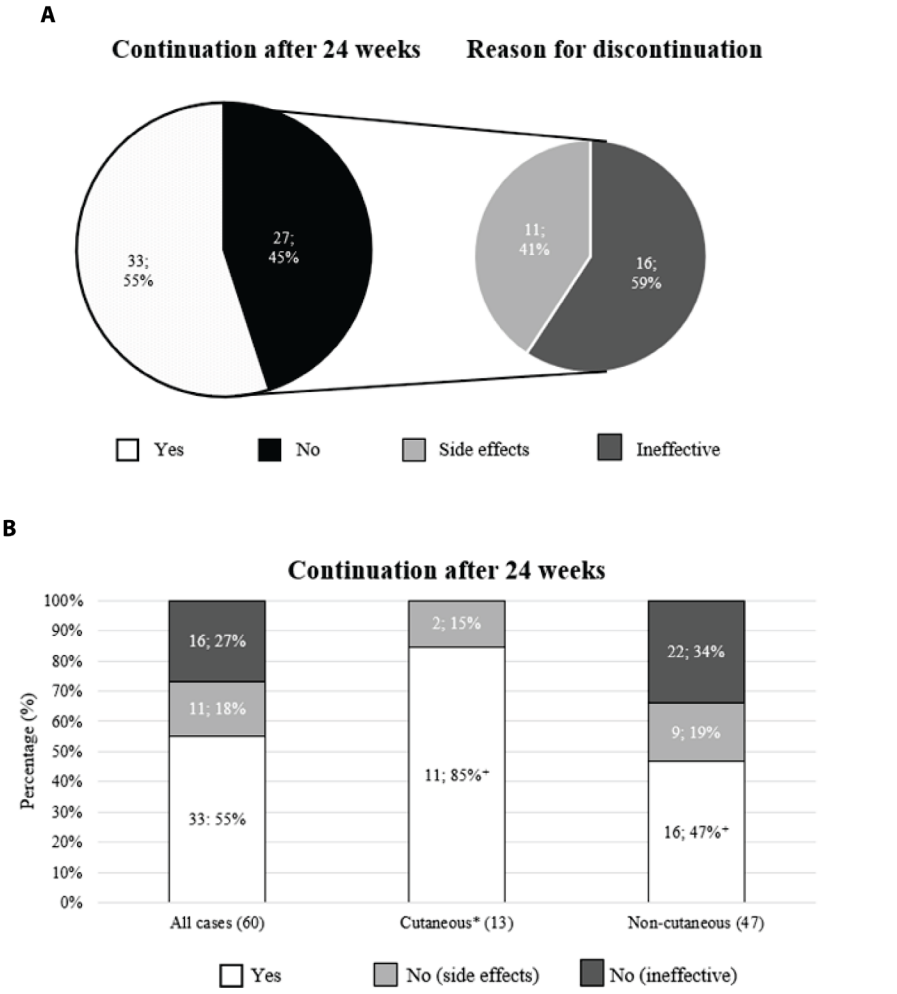

Figure 2. A. Continuation of HCQ after 24 weeks and reason for discontinuation (N, %). **B.** HCQ Continuation and discontinuation (due to ineffectiveness and side effects) after 24 weeks, total and by subgroup (N, %). +Difference in continuation between cutaneous and non-cutaneous patients, p=0.02. *With or without musculoskeletal symptoms.

cutaneous manifestations. Based on our chosen primary endpoint of continuation HCQ after 24 weeks, our data suggest that therapy is satisfactory in 33 patients (55%) with sarcoidosis that is not threatening vital internal organs such as heart, central nervous system or lungs. Our study demonstrates that HCQ is especially effective in the treatment of cutaneous sarcoidosis. Positive results of HCQ in cutaneous sarcoidosis are also seen in previous (case) reports (6–9,13,17).

In our cohort, 24 patients (40%) reported side effects and 11 patients (18%) discontinued because of these. The degree of reported side effects was lower compared with a study in sarcoidosis patients using either prednisone or methotrexate (MTX) (78% and 49% respectively) (2). However, in another study comparing MTX with Azathioprine as a second-line treatment for sarcoidosis, 16% of the patients discontinued MTX due to side effects and 25% of patients discontinued Azathioprine for this reason (18). In our study, 18% of patients discontinued HCQ based on side effects. Therefore, when we compare this with the previously mentioned 16% of patients discontinuing MTX in sarcoidosis, this suggests that HCQ might not be as well tolerated in daily clinical practice as sometimes thought. However, lacking prospective data on side effects compromises a proper comparison. Furthermore, patients with sarcoidosis

Table 2. Side effects of HCQ

Side effects HCQ	**Side effects**	**Leading to discontinuation**
Number of patients (N, %)	**24 (40)**	**11 (18)**
Gastro-intestinal	**10 (17)**	**5 (8)**
Nausea	5 (8)	3 (5)
Diarrhoea	2 (3)	0 (0)
Flatulence	2 (3)	0 (0)
Dyspepsia	2 (3)	1 (2)
Abdominal cramps	2 (3)	1 (2)
Cutaneous	**6 (10)**	**3 (5)**
Hair loss	2 (3)	1 (2)
Itches	2 (3)	2 (3)
Increased swelling and pain	1 (2)	0 (0)
'other'	**14 (23)**	**13 (22)**
Non-severe eye symptoms	3 (5)	1 (2)
Headache	2 (3)	2 (3)
Negative effect on mood	2 (3)	2 (3)
Heart palpitations	2 (3)	1 (2)
Agitated	1 (2)	1 (2)
Tinnitus	1 (2)	1 (2)
Abnormal liver values	1 (2)	1 (2)
Hypoglycaemia with pre-existing DM2	1 (2)	0 (0)
General malaise	1 (2)	0 (0)
Somnolence	1 (2)	0 (0)
Epistaxis	1 (2)	0 (0)
Neurological symptoms (nerve conduction disorders, tingling, peripheral nerve pain)	1 (2)	1 (2)
Dizziness	1 (2)	0 (0)
Concentration problems	1 (2)	0 (0)
Tightness in throat	1 (2)	0 (0)
Hyperhidrosis	1 (2)	1 (2)
Hearing loss	1 (2)	1 (2)
Vaginal fungal infections	1 (2)	0 (0)

Abbreviation: N: number.

that is not threatening vital internal organs might be less willing to continue drugs with side effects than for instance patients with severe sarcoidosis, the latter being more often treated with MTX. Although the optimal dosing regimen in sarcoidosis patients is unknown, international rheumatology guidelines suggest not more than 5mg/kg with a maximum of 400mg/day to avoid retinal toxicity (19). Additionally, risk of QTc prolongation is rare, but increased monitoring or potentially avoiding HCQ might be appropriate in patients concurrently using other QTc prolonging drugs.

A limitation of this study was that due to its retrospective nature, no established tools such as the Sarcoidosis Activity and Severity Index (SASI) or Health-Related Quality of Life (HRQoL) questionnaires could be used to quantify results (20,21). The predominant strength of this study is a relatively large cohort of sarcoidosis patients on monotherapy HCQ. Other strengths were the clear results about indications,

differences of continuation rates in various groups and the level of tolerability in a real-world setting.

In conclusion, our data demonstrates that HCQ monotherapy was predominantly initiated in our centre for cutaneous lesions or musculoskeletal related pain in sarcoidosis. HCQ seems to be predominantly effective in treatment of cutaneous sarcoidosis. Finally, based on reported side-effects and discontinuation of therapy, HCQ might not be as well tolerated as previously thought in clinical practice. Future randomised trials are needed to see which kind of therapy is most effective and best tolerated in the treatment of non-vital-organ-threatening but clinically relevant symptoms in sarcoidosis.

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