Concise Report

Treatment of sicca symptoms with hydroxychloroquine in patients with Sjögren’s syndrome

Markus Rihl1, Kai Ulbricht1, Reinhold E. Schmidt1 and Torsten Witte1

Objective. There is no established disease-modifying treatment of xerostomia and xerophthalmia in SS. This retrospective study was performed in order to evaluate the efficacy of HCQ for glandular function, i.e. saliva and tear production.

Methods. Fourteen patients with primary SS (pSS) were included (Group A). All patients were anti-Ro and/or -La antibody positive except one. Patients were treated with HCQ for a period of up to 6 months. Glandular function was determined by Saxon’s and Schirmer’s tests for the dominant eye at baseline and at the end of the treatment. We included a control group of 21 patients with objective sicca symptoms and positive α-fodrin antibodies (Group B).

Results. In patients with pSS (Group A), a significant increase in saliva production after HCQ treatment \( P = 0.022 \) was observed. A subanalysis revealed that particularly the α-fodrin-positive patients responded to HCQ \( P = 0.017 \) α-fodrin positive vs \( P = 0.4 \) α-fodrin negative. Interestingly, patients with sicca symptoms and α-fodrin antibodies (Group B) showed a significant increase in tear production \( P = 0.001 \). In addition, there was a positive correlation between the α-fodrin IgA antibody concentration and the Schirmer’s test at baseline \( r = 0.66; P = 0.001 \) and after treatment \( r = 0.6; P = 0.004 \) in this group.

Conclusions. HCQ treatment led to a beneficial effect on xerostomia in patients with pSS who lack severe organ manifestations. The response was greater in α-fodrin-positive patients.

Key words: Sjögren’s syndrome, Sicca symptoms, Hydroxychloroquine, α-Fodrin.

Introduction

Primary SS (pSS) is a chronic inflammatory autoimmune disorder leading to dryness of eyes and mouth related to a reduced lacrimal and salivary gland function. This is referred to as sicca symptoms. In addition, a wide spectrum of extraglandular disease manifestations such as musculoskeletal disorders, RP, vasculitis, pulmonary hypertension and neurological involvement may occur [1]. The classification criteria comprise both subjective and objective sicca symptoms, parotid gland inflammation, a positive histology and autoantibodies against Ro/SSA and La/SSB antigens that are known to have a rather low sensitivity [2]. More recently, autoantibodies against α-fodrin have been introduced in the diagnosis of SS [3]. There is evidence that α-fodrin antibodies might be a valuable diagnostic marker in anti-Ro antibody-negative patients with pSS [4, 5]. It has also been postulated that the presence of α-fodrin antibodies might indicate an active glandular inflammation [6].

There is no established disease-modifying treatment of objective ocular and oral dryness although a variety of agents has been investigated [7, 8, 10–12]. The generally well-tolerated antimalarial agent HCQ has been reported to improve laboratory markers of inflammation, but its effect on glandular function has not been investigated in prospective, clinical trials. However, an earlier retrospective study reported an improvement of the lacrimal function [13]. In addition, HCQ showed favourable effects in children [14], whereas other studies failed to show a beneficial effect [15].

In this retrospective analysis, we used HCQ treatment over a period of 3–9 months for patients with pSS presenting with sicca symptoms as the major clinical aspect but lacking severe organ manifestations. Glandular function tests were performed at baseline and after treatment.

Patients and methods

We performed a retrospective analysis on 14 patients with pSS fulfilling the classification criteria established by the European-American Consensus Group (Group A, Table 1) [16]. Patients were seen consecutively in our outpatient clinic between 2002 and January 2008, and offered a treatment with HCQ after severe organ manifestations had been excluded. All patients were females, their mean age was 56 (±s.d. 12.4; range 36–79) years, they were all ANA positive, 13/14 patients were anti-Ro antibody positive. Eight patients were positive for α-fodrin IgG and/or IgA at baseline. One patient was anti-Ro antibody negative and was diagnosed according to a positive histology, this patient was also α-fodrin antibody positive. All patients were exclusively treated with HCQ over a mean period of 4.9 (±s.d. 1.1; range 3.5–6) months due to extraglandular manifestations comprising of mainly arthralgia and/or fatigue. The dosage was adjusted to body weight, i.e. 300 and 400 mg/day for patients with a body weight between 50–64 and >64 kg, respectively. No other systemic medication was administered.

For comparison, we also analysed a cohort of 21 patients with ocular and/or oral dryness being α-fodrin antibody positive but anti-Ro/La antibody negative (Group B, Table 1). Eighteen out of 21 patients were females, their mean age was 55 (±s.d. 15.1; range 23–83) years. Currently, there is no disease classification for such a cohort. However, 10/21 (48%) patients were ANA positive and might thus be classified as UCTD. They were treated with HCQ due to extraglandular manifestations such as arthralgia or myalgia in most cases. The ANA-negative patients were informed about the diagnostic situation and also offered a treatment with HCQ due to extraglandular manifestations and fatigue symptoms. These patients were also treated exclusively with HCQ over a mean period of 5.2 (±s.d. 1.0; range 3–6.5) months.

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α-Fodrin antibody concentrations in the serum were measured using a commercially available ELISA kit (Aesku.Diagnostics, Wendelsheim, Germany). This method was validated earlier [4].

Spontaneous saliva and tear production using the Saxon’s test (defined as the weight of saliva produced in 2 min while chewing on a gauze sponge, normal value >3.5 g) [4] and the Schirmer’s test (tear flow over 5 min of both eyes, normal value >5 mm) [4] was measured at baseline and at the end of the treatment. Values of the Schirmer’s test were used for the dominant eye, i.e. the eye with the lower tear flow at baseline. When the values were identical for both eyes, the value of the left eye was chosen arbitrarily. Values were subjected to the Wilcoxon signed-rank test for related samples, a \(P\)-value of <0.05 was considered significant. Correlations were performed using the Spearman’s rho test. Written informed consent was obtained from all patients included in the analysis. The study was performed according to the Declaration of Helsinki and was approved by the local ethical committee (Ethikkommission MHH).

Results

Data are given as mean ± s.d. Baseline characteristics of all analysed patients were similar. HCQ was well tolerated, there were no documented side effects and no discontinuations of the drug. None of our patients in this analysis had severe organ manifestations that would have required a more potent immunomodulating agent.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=14)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Fodrin IgG, IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>s.d.</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Range</td>
<td>1–89</td>
<td>1–43</td>
</tr>
<tr>
<td>α-Fodrin IgA, IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>s.d.</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Range</td>
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<td>1–78</td>
</tr>
<tr>
<td>Saxon (g/2 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>3.4 (^a)</td>
</tr>
<tr>
<td>Median</td>
<td>2.7</td>
<td>3.1</td>
</tr>
<tr>
<td>s.d.</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
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<td>0.7–8.3</td>
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<tr>
<td>Schirmer (mm/5 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Median</td>
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<td>1.0</td>
</tr>
<tr>
<td>s.d.</td>
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<td>15.1</td>
</tr>
<tr>
<td>Range</td>
<td>0.0–8.0</td>
<td>0.0–35.0</td>
</tr>
</tbody>
</table>

Ig: immunoglobulin. This table depicts the values for the mean, median, s.d. and the range of parameters determined at baseline and after a treatment with HCQ over a mean period of 4.9 and 5.2 months in Groups A and B, respectively. The level of significance was determined using the Wilcoxon signed-rank test. Values significantly altered after treatment are printed in bold: in Group A, the saliva production was increased (\(P=0.02\)) as was the tear production in Group B (\(P=0.001\)).

![Fig. 1. Glandular function, i.e. Saxon’s (A, B) and Schirmer’s test (C) values are depicted at baseline and after treatment with HCQ in patients with SS (Group A, n=14). The Saxon’s test values were subanalysed according to the patient’s α-fodrin status. The α-fodrin antibody-positive subgroup (A, n=8) revealed a significant increase in saliva production as measured by the Schirmer’s test (\(P=0.017\)). The dotted lines indicate the thresholds in regard to a residual glandular function, i.e. >1 g for the Saxon’s and ≥1 mm for the Schirmer’s test, respectively.](image-url)
The mean glandular function test value at baseline was $2.9 \pm 2.4$ (range 0.3–8) g for the saliva and $2.3 \pm 2.8$ (range 0–7) mm tear production of the dominant eye. After a mean treatment period with HCQ of $4.9 \pm 1.1$ (range 3–6) months, the saliva production was significantly increased to $3.4 \pm 2.3$ (range 0.7–8.3) g ($P = 0.022$) as measured by the Saxon’s test. Apart from CRP, which significantly decreased after treatment, all other parameters (Schirmer’s test, ANA, RF, α-fodrin IgG and IgA) were unchanged. Saliva and tear production increased in 10/14 patients and in 7/14 patients, respectively. The majority of patients with a residual saliva production (i.e. $>1$ g/2 mm) at baseline (n = 10 patients) improved after treatment (n = 7/10) and of note, the majority of this subgroup was α-fodrin (IgG and/or IgA) positive (n = 6/7). Finally, a subanalysis of all patients in Group A revealed that particularly the α-fodrin-positive subgroup of patients responded to HCQ ($P = 0.017$ vs $P = 0.4$ in α-fodrin-negative patients) (Fig. 1).

In Group B, the mean age of the 21 Ro-negative patients (18 women, 3 men) with objective dryness and α-fodrin antibodies was $55 \pm 15$ (range 23–83) years (Group B, Table 1). All patients were positive for IgG and/or IgA α-fodrin antibodies. The mean glandular function test values at baseline were $4.3 \pm 2.3$ (range 0.2–8.6) g for saliva production and $4.9 \pm 5.9$ (range 0–23) mm for tear production of the dominant eye (Table 1). The mean treatment period was 5.0 ± 1.0 (range 3–6) months. After HCQ treatment, there was no difference in saliva production, however, the values of the Schirmer’s test (dominant eye) were significantly increased to $14.9 \pm 12.3$ (range 0–35) mm ($P = 0.001$) (Table 1, Fig. 2). Saliva and tear production increased in 15/21 patients and in 16/21 patients, respectively. This treatment response was independent of a residual tear flow.

Of note, there were significant correlations between α-fodrin IgA concentrations and Schirmer’s test values at baseline ($r = 0.66, P = 0.001$) as well as after treatment ($r = 0.6, P = 0.004$).

Discussion

The majority of drugs reported for treating subjective sicca symptoms in patients with pSS seem to have a considerable placebo effect. In addition, most agents failed to show an improvement of the objective glandular function. Our retrospective analysis of patients with pSS demonstrates for the first time that HCQ was also able to significantly improve the saliva production. This effect was even greater when the patients were analysed according to their α-fodrin antibody status revealing a more pronounced improvement in α-fodrin-positive patients. Antibodies against α-fodrin have been shown to be associated with the inflammatory activity of pSS and at least in one study with the disease duration [17]. HCQ could be beneficial in this subgroup of patients, because the anti-inflammatory function may be exerted more effectively in patients with a higher inflammatory activity. Along this line, the presence of α-fodrin antibodies was associated with a propensity of a slightly higher residual saliva production at baseline (mean saliva production at BL 3.3 ± 2.4 g in α-fodrin-positive patients vs 2.3 ± 2.5 g in α-fodrin-negative patients) and a significant improvement of saliva production due to HCQ treatment. However, the mode of action of HCQ in pSS is not clear. In vitro data postulate an effect mediated by an inhibition of the glandular cholinesterase activity [18].

In conclusion, α-fodrin antibodies may function as a predictive marker for the response to treatment with HCQ.

Of interest, we found a highly significant improvement of the lacrimal function, i.e. the xerophthalmia of the dominant eye in the patient cohort with UCTD and sicca symptoms being negative for anti-Ro/-La but positive for α-fodrin antibodies. This effect was not related to a residual tear flow. The significant correlations in this cohort observed between α-fodrin IgA concentrations and the Schirmer’s test values also underline the hypothesis that the presence of α-fodrin antibodies could be associated with an active glandular inflammation.

The limitations of this small open label study should also be stated here. They are mostly due the nature of a retrospective analysis that lacks a placebo arm. In addition, there might be a bias due to the selection of a cohort with a generally mild disease. Another critical issue is the question of the clinical relevance of the observed increase of saliva and tear production since we did not document the subjective sicca symptoms. Accordingly, the results should be read with caution. However, this study emphasizes that HCQ is well tolerated and beneficial particularly in an α-fodrin antibody-positive subgroup of patients with pSS.

### Rheumatology key messages

- Patients with pSS were treated with HCQ for 5 months.
- There was a significant increase of saliva production.
- This positive effect was pronounced in the α-fodrin antibody-positive subgroup.

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References