# Do antimalarials protect against damage accrual in primary Sjögren's syndrome? Results from a Latin-American retrospective cohort

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## ABSTRACT

**Objective.** *To assess the use of antimalarials and to evaluate their association with damage accrual in a Latino-American cohort of patients with primary Sjögren's syndrome (pSS).*

**Methods.** *We included 377 patients attending three tertiary referral centres from: Argentina (n=110), Brazil (n=49) and Mexico (n=218). We retrospectively registered demographics, disease duration and use of prednisone (PDN), immunosupressors and antimalarials. We scored the cumulative ESSDAI and the SSDDI at last follow-up.*

**Results.** *Most patients were females, median disease duration 6 years, mean SSDDI score 2.7±1.8, mean cumulative ESSDAI score 9.3±8.3, 39% used PDN and 37.4% immunosupressors. A total of 191 patients (50.6%) had ever used antimalarials, mean use 43.5±40 months, being the main indication arthritis. These patients had a longer disease duration, used more PDN and immunosupressors and had lower SSDDI scores. The pleuro-pulmonary domain was significant different among groups (6.7% antimalarials users vs. 14.9% not users, p=0.01). At the logistic regression, the pleuro-pulmonary domain (OR 0.37, 95% CI 0.17-0.78, p=0.01), the age (OR 0.97, 95% CI 0.96-0.99, p=0.01) and the disease duration (OR 1.07, 95% CI 1.03-1.1, p=0.0001) were associated with antimalarials use. When we compared patients with a SSDDI ≥3 vs. SSDDI<3, in the multivariate analysis the use of antimalarial was protective (OR 0.58, 0.36-0.93 CI 95%, p=0.02) and the cumulative ESSDAI a risk factor for damage accrual (OR 1.1, 1.07-1.15 CI 95%, p<0.001).*

**Conclusion.** *Antimalarials were frequently used in pSS and seemed to protect against damage accrual, specifically at the pleuro-pulmonary domain. This finding should be confirmed in prospective studies.*

## Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disorder mainly affecting the exocrine glands, leading to keratoconjunctivitis sicca and xerostomia. Nevertheless, the current concept is that pSS is a systemic disease with a high prevalence of extra-glandular features (1); and in this context, patients might acquire accrual damage. In a cohort of 148 pSS patients with a median follow-up of 10 years, the total increase of patients with damage was 28.3% after 1 year, 36.7% after 5 years and 45% at the end of the study (2). Nevertheless, as only few studies have assessed the presence of damage accrual in pSS; it is important to identify predictors as well as protective factors for damage in these patients.

Antimalarials (specially hydroxycloroquine) are frequently used in pSS (2-5). Their use range from 30 to 50%, being their main indication articular involvement (5). However, these drugs have failed to demonstrate an impact in dry eye and mouth symptoms in clinical trials (2-4).

The aim of this study was to assess the use of antimalarials and to evaluate their association with damage accrual in a Latino-American cohort of patients with pSS.

## Methods

We included 377 consecutive patients with the diagnosis of pSS according to the American-European Consensus Group criteria (6), attending to three tertiary referral centres from three countries: Argentina, Brazil and Mexico.

Patients' clinical records were care-

fully reviewed according to a pre-established protocol. We retrospectively registered demographics, age at disease onset, disease duration, ever use of prednisone (PDN), immunosupressors and antimalarials (chloroquine or hydroxychloroquine). We registered their time of use, dose and main indication of antimalarials.

We also scored the cumulative activity during the follow-up using the cumulative ESSDAI at the last visit, as well as the damage accrual using the SSDDI also at the last follow-up (7). Briefly, the SSDDI includes the following domains (maximum total score=16): oral, ocular, neurologic, pleuro-pulmonary, renal and lymphoproliferative.

*Statistical analysis*

We used descriptive statistics. Comparison between means was made with Student's *t*-test. Categorical variables were analysed with Chi square test and logistic regression analysis reporting OR and 95% CI. A two-tailed $p<0.05$ was considered statistically significant. All analyses were performed using the SPSS for Windows 20.0.

## Results

We included 377 patients, 218 from Mexico, 110 from Argentina and 49 from Brazil. Most of the patients were females (97.3%) with a mean age at diagnosis of 48.9±12.7 years, mean age at last follow-up 56.7±13.2 years and median disease duration 6 years. Among the cohort, 87 patients (23.1%) had hypertension, 62/375 (16.5%) dyslipidaemia, 25 (6.6%) diabetes mellitus and 16 patients (4.2%) cardiovascular disease. The mean cumulative ESSDAI score was 9.3±8.3 and the median SSDDI score was 2 (0-10). The involvement of each domain of the SSDDI was as follows: oral 292/334 (87.4%), ocular 297/352 (84.4%), neurological 57 (15.1%), pleuro-pulmonary 40/374 (10.7%), renal 21/275 (5.6%) and lymphoproliferative 12 (3.2%).

Table I shows the demographic and clinical characteristics of the patients according to their country. Mexican patients had a longer follow-up, more use of prednisone and had a higher cumulative ESSDAI. Patients from Argentina were older at disease onset and use more frequently immuosuppressors, whereas patients from Brazil had lower SSDDI scores and most of them used antimalarials (Table I).

**Table I.** Clinical features among 377 patients with primary Sjögren's syndrome.

| | Mexico n=218 | Argentina n=110 | Brazil n=49 | *p*-value |
|---|---|---|---|---|
| Age at diagnosis | 47.2 ± 12.9 | 52.5 ± 10.8 | 47.1 ± 13.1 | 0.01 |
| Disease duration in years | 8.7 ± 8.0 | 5.5 ± 5.5 | 4.8 ± 4.2 | 0.03 |
| Female, n (%) | 212 (97.2) | 107 (97.3) | 48 (98) | 0.96 |
| Follow up in years | 8.7 ± 87 (0-44) | 5.5 ± 5(0-19) | 4.8 ± 4.2 (0-25) | 0.01 |
| Prednisone use, n (%) | 102 (46.8) | 29 (26.4) | 16 (32.7) | 0.01 |
| Immunosuppressors use, n (%) | 98 (45) | 7 (6.4) | 36 (73.5) | 0.01 |
| Antimalarials use, n (%) | 107 (49.1) | 48 (43.6) | 39 (79.6) | 0.01 |
| SSDDI score (last visit) | 2.8 ± 2 | 3 ± 1.6 | 1.8 ± 1.3 | 0.01 |
| Cumulative ESSDAI score | 10.8 ± 8.9 | 7.5 ± 6.7 | 6.7 ± 7.2 | 0.01 |

Values represent mean ± SD unless otherwise indicated.

**Table II.** Clinical features according their antimalarial status.

| | Use of antimalarials n=191 | Without antimalarials n=186 | *p*-value |
|---|---|---|---|
| Female, n (%) | 187 (97.9) | 180 (96.8) | 0.53 |
| Disease duration years | 8.4 ± 7.1 | 5.9 ± 6.6 | 0.0001 |
| Age at last follow-up | 55.3 ± 12.9 | 57.8 ± 13.3 | 0.09 |
| Diabetes, n (%) | 16 (0.3) | 9 (4.8) | 0.21 |
| Hypertension, n (%) | 42 (21.9) | 45 (24.2) | 0.61 |
| Dyslipidaemia, n (%) | 31 (16.2) | 31 (16.8) | 1 |
| Cardiovascular disease, n (%) | 6 (3.1) | 10 (5.3) | 0.09 |
| Cumulative ESSDAI score | 9.1 ± 7.3 | 9.4 ± 9.2 | 0.68 |
| SSDDI score (last visit) | 2.4 ± 1.7 | 2.9 ± 1.8 | 0.01 |
| Prednisone use, n (%) | 85 (44.5) | 62 (33.3) | 0.02 |
| Immunosuppressors use, n (%) | 84 (43.9) | 57 (30.6) | 0.007 |
| Oral domain, n (%) | 147/174 (84.5) | 145/160 (90.6) | 0.13 |
| Ocular domain, n (%) | 151/185 (81.6) | 146/167 (87.4) | 0.13 |
| Neurological domain, n (%) | 27 (14.1) | 30 (16.1) | 0.50 |
| Pulmonary domain, n (%) | 13/190 (6.8) | 27/184 (14.7) | 0.01 |
| Renal domain, n (%) | 7/190 (3.7) | 14/185 (7.6) | 0.10 |
| Lymphoproliferative domain, n (%) | 6 (3.1) | 6 (3.2) | 0.91 |
| Country | | | |
| Mexico, n (%) | 105 (55) | 113 (60.2) | 0.0001 |
| Argentina, n (%) | 48 (25.1) | 62 (33.3) | |
| Brazil, n (%) | 38 (19.9) | 11 (5.9) | |

Values represent mean ± SD unless otherwise indicated.

A total of 147 patients (38.9%) had ever used PDN and 141(37.4%) immunosupressors. Whereas a total of 191 patients (50.6%) had ever used antimalarials: chloroquine 37 patients and hydroxychloroquine 178 patients (non-exclusive groups). The indications were arthritis (n=124, 65.4%), parotid enlargement (n=12, 6.2%), only sicca symptoms (n=37, 19.3%) and other causes (n=17; 8.9%) including purpura or fatigue. The median dose for hydroxychloroquine was 400 mg/day (range 200–400 mg) and for chloroquine was 150 mg (range 150–300), and the overall mean time of use of antimalarials was 43.5±40 months.

When we compared patients with and without ever use of antimalarials (Table II), the presence of comorbidities including cardiovascular events were similar, whereas patients who used antimalarials had a longer disease duration, used more frequently PDN and immunosupressors and had a lower SSDDI score.

As shown in Table II, the pulmonary domain was the only one with a significant difference among groups (6.7% among

the patients who used antimalarials *vs*. 14.9% without antimalarials, $p$=0.01).

At the logistic regression analysis, the variables that remained associated with use of antimalarials were pleuro-pulmonary domain (OR 0.37, 95% CI 0.17–0.78, $p$=0.01), age (OR 0.97, 95% CI 0.96–0.99, $p$=0.01) and disease duration (OR 1.07, 95% CI 1.03–1.1, $p$=0.0001).

In order to evaluate the variables associated with damage, we established an arbitrary cut-off ≥3 for the SSDDI (as the median overall SSDDI in the cohort was 2 points). We compared patients with a SSDDI ≥3 (n=170) compared with those SSDDI<3 (n=207) were older (59.1±12.6 *vs*. 54.6±13.2 years, $p$=0.001), had a longer follow up (8.04±7.9 *vs*. 6.5±6.1 years, $p$=0.02), a higher cumulative ESSDAI score (12.4±9.3 *vs*. 6.7±6.2, $p$=0.0001) and used less antimalarials (42.9% *vs*. 57%, $p$=0.007). The use of prednisone (42.5% *vs*. 35.7%, $p$=0.15) and immunosupressors (34.7% *vs*. 39.6%, $p$=0.33) were similar among the group of patients with SSDDI ≥3 *vs*. SSDDI<3.

At the logistic regression analysis adjusted by country and disease duration, the following variables remained as independent predictors of damage (SSDDI ≥3): use of antimalarial (OR 0.58, 95% CI 0.36–0.93, $p$=0.02) and cumulative ESSDAI (OR 1.1, 95% CI 1.07–1.15, $p$<0.001).

## Discussion

In a real-world population-based study on more than 10,000 SS patients, pharmacological therapies during the first year post diagnosis, consisted mainly of symptomatic drugs and traditional immunosuppressive therapies (8). In this scenario, antimalarials specially hydroxychloroquine, are frequently prescribed in pSS. For instance in a Spanish multicentre study of 1120 patients, 25% of the cases were under hydroxychloroquine treatment (9); whereas in Italian population a higher percentage (40.8%) received them (10) as well as in a Mexican cohort where almost half of the patients received them (5). In the present study, now including three Latin-American countries, the percentage of patients receiving antimalarials ranged from 43.6 to 79.6%. This difference could reflect different presentations of the disease in different ethnic groups or more probably different criteria for indication across different rheumatologist due to the lack of evidence based guidelines.

In general antimalarials are well tolerated and rarely need to be discontinued, ranging their toxicity from 18.4–35.8% among pSS patients (5, 10). However they might cause irreversible damage to retina, especially if taken in high doses or for a long time. In this regard, in a previous work, we observed toxicity in 9.7% of pSS patients, being the causes: gastrointestinal symptoms, skin hyperpigmentation and ophthalmologic deposits (5). Similar adverse events, mostly related to non-ophthalmologic reasons were also reported in an Italian cohort (10). Furthermore in that population, the incidence rate of global discontinuation was 6.34 per 1,000 patient-year. And the reasons for discontinuation were: lack of efficacy in 11%, adverse events in 35.8%, non-compliance 41% and miscellaneous causes in 13%. Interesting, discontinuation due to adverse events occurred after few months of treatment; whereas discontinuation due to lack of efficacy and to non-compliance were documented later over the follow-up (10).

Initially some studies regarding the use of antimalarials in pSS showed improvement in dry eye symptoms (11), as well as augmentation of saliva production (12). Nevertheless, clinical trials later indicated that antimalarials do not improve sicca symptoms (3-4); being nowadays their main indication the presence of arthritis (5) as corroborated in this study. Furthermore, recent studies had revealed that hydroxychloroquine is associated with lower risk of death and lymphoma (9), as well with a lower risk of hospitalisation in pSS (13).

Few studies have evaluated damage in pSS. For instance, Krylova *et al*. noticed a moderate increase of damage after following 60 patients with pSS for 10 years. In their study, damage accrual was present in 45%, and mostly due to the ocular domain, parotid swelling and malignancy categories. Indeed there was a 6-fold increase in the malignancy damage compared with the 2-fold increase in the total damage score (2). Furthermore, in a Dutch cohort of 110 patients with pSS, the presence of extraglandular damage according to a modified SSDDI (excluding oral and ocular domain, but including primary biliary cirrhosis, pernicious anaemia, Hashimoto's disease and vitiligo) was assessed. That study reported that 44.5% of the patients had at least one organ involved, 5.4% two organs and 0.9% three organs. The most frequently positive items accounting for damage were polyneuropathy (17.3%), pleuro-pulmonary involvement (11.8%), Hashimoto's disease (9.1%) and mucosa-associated lymphoid tissue (MALT) lymphoma (1.8%).

However, the mean number of involved organs per patient after a median follow-up of more than 8 years was low (0.6 organs) (14).

In contrast, in our study we found higher SSDDI scores, but it is important to highlight that we also considered both ocular and oral components, that indeed were the most prevalent domains. On the other hand, we also found that the main extraglandular domain with damage was the neurological. In our study we also observed in 10.7% of the patients pleuro-pulmonary damage, a finding that is concordant with previous reports. In the study of Ter Borg *et al*., pleuro-pulmonary damage was present in 11.8% of cases (14). Recently, a higher prevalence of pleuro-pulmonary damage (22%) was reported in a population-based hospital cohort with pSS (15).

Our analyses suggested that the use of antimalarials, might exert a protective effect in terms of damage accrual. This has not been previously reported in patients with pSS. However, similarly in SLE patients, antimalarials have proved to improve survival and retard damage accrual (16, 17). The precise mechanism by which antimalarials might influence damage in autoimmune disease is still unknown, but their anti-inflammatory and immunomodulatory properties have been recognised. Antimalarials have numerous and complex mechanisms of action, such as blocking of antigen presentation, T-cell stim-

ulation, inhibition of IL-1, IL-6- IL-17, IL-22, TNF, IFN alpha and gamma as well as toll-like receptors; and they also induce apoptosis and inhibit endosomal acidification (17).

Specifically, in pSS population, hydroxychloroquine has been associated with the reduction of erythrocyte sedimentation rate (4), serum γ-globulins, serum IL-6 levels, salivary and serum BAFF levels (18, 19) as well as salivary levels of cholinesterase (20).

Herein we observed that the protection for damage was driven by the pleuropulmonary domain. This domain has been associated with an impaired quality of life and physical capacity and to a reduced 10-year survival (15). In this regard, antimalarials have been used as an off-label treatment in primary interstitial pulmonary disease in children in a dose of 6-10 mg/kg/day (21); but so far, there are no controlled studies on this topic. However, antimalarials are not considered standard treatment for severe extra glandular involvement, and this change in the pleuro-pulmonary domain could reflect rather a preventive effect. Furthermore because our study design, we are not able to establish a temporal relationship between the antimalarials use and pleuro-pulmonary involvement; and this difference indeed could be secondary to an indication bias where patients with less severe disease tend to receive more antimalarials. However, patients who used antimalarials also received more frequently prednisone and immunosuppressors, which can be interpreted as a subrogated for severe disease. Moreover the interaction and effect on damage of multiple treatments could be difficult to dissect; however it is important to highlight that when we compared patients with higher damage (SSDDI ≥3) antimalarials remained as a protective factor for damage, even when adjusted for use of prednisone or other immunosuppressors.

Finally, an increased frequency of CV disease has been associated with SS in some studies (8, 22). Herein due to our low prevalence of cardiovascular events, we were not able to explore properly their association with the use of antimalarials.

## Conclusions

Our study has however some limitations, and first of all its retrospective design. Even if we have adjusted our final model for possible confounders, such as cumulative disease activity, it is still possible that our results may be affected by confounding severity bias, as previously mentioned. Nevertheless, our work is the first one to explore this topic, and the mechanisms of action of antimalarials, and already existing experience in other diseases, such as SLE, may make our findings biologically plausible.

In summing up, antimalarials have been frequently used in this Latin-American cohort of patients with pSS, and seem to protect against damage accrual, specifically at the pleuro-pulmonary domain. However, this finding should be confirmed in prospective studies to shed more light on this topic.

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