Use and withdrawal of immunosuppressors in primary Sjögren's syndrome

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ABSTRACT

Objective. *To assess the use and causes of withdrawal of glucocorticoids and immunosuppressors among patients with primary Sjögren's syndrome (pSS) in the clinical setting.*

Methods. *We retrospectively reviewed the medical records of 155 pSS patients and registered demographics, glandular/extraglandular features, serological data, cumulative ESSDAI and SSDDI. A single rheumatologist attributed the indication and cause of withdrawal of glucocorticoids and immunosuppressors.*

Results. *92.2% of the patients were female, mean age 57.4±14.7 years and median follow-up 11 years. One hundred and four (67%) patients received glucocorticoids and/or immunosuppressors: 3.8% only glucocorticoids, 43.9% only immunosuppressors and 56.5% their combination. The most used drugs were antimalarials (46.4%), prednisone (36.7%), azathioprine (AZA) (23.8%) and methotrexate (MTX) (18%). At the multivariate analysis, the presence of non-erosive arthritis OR 5.02 (95% CI 1.74–14.47, p=0.003) and the median cumulative ESSDAI score OR 1.10 (95% CI 1.03–1.17, p=0.002) were associated with the use of these drugs. The causes of withdrawal were: 39% improvement, 35.2% patient's own decision, 18.1% toxicity and 11% lack of efficacy. We found toxicity in 14.2% MTX users, 9.7% for AZA, 9.7% for antimalarials and 7.6% for cyclophosphamide.*

Conclusion. *More than half the patients received glucocorticoids and/or immunosuppressors and a not negligible number decided on their own to suspend them, alerting physicians of secondary adverse events and tolerability.*

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune epithelitis that affects around 1% of general population, especially middle age or elderly women (1). The disease was originally considered to have a benign course and low mortality. Nevertheless, the current concept is that pSS is a systemic disease with a high prevalence of extraglandular manifestations including fatigue, Raynaud, articular features, vasculitis, cytopenias, pulmonary, renal and neurological involvement (1-4).

The treatment of pSS is largely based on alleviation of oral and ocular symptoms; however in some patients there is a need of systemic therapy including glucocorticoids and immunosuppressors (1, 5, 6). A retrospective cohort that included 21 Spanish centres (1120 patients), recently evaluated the use of glucocorticoids and immunosuppressors for treating systemic features. This study reported that 42% of the patients were under steroids, 25% patients received antimalarials and 13% immunosuppressors (7).

Although immunosuppressors are commonly used to treat systemic manifestations of pSS, there is a lack of information regarding their safety and tolerance. The objective of this study was to assess the use and causes of withdrawal of immunosuppressors and glucocorticoids among a cohort of patients with pSS in the routinely rheumatologic clinical practice.

Patients and methods

This is a retrospective cohort study that included 155 consecutive patients with pSS who regularly attended the Instituto Nacional de Ciencias Médicas y Nutrición SZ, a tertiary referral hospital from 2010–2014. All the patients fulfilled the 2002 classification criteria for pSS (8). We excluded patients with any other concomitant connective tissue disease.

Patients' clinical records were carefully reviewed according to a pre-established protocol. We retrospectively collected demographics, age at diagnosis, length of follow-up, as well as clinical and

serological data such as ocular tests (Schirmer, fluorescein staining), non-stimulated whole salivary flow, parotid enlargement, anti-Ro/SSA and anti-La/SSB antibodies, rheumatoid factor (RF), antinuclear antibodies (ANA), hypergammaglobulinaemia and hypocomplementaemia ever.

We registered the following glandular (oral and ocular sicca symptoms, parotid enlargement) and extraglandular manifestations: non-erosive arthritis, skin vasculitis (palpable purpura or biopsy proven), lymphadenopathy, interstitial lung disease (confirmed by x-ray or high resolution CT scan and/or histology, altered pattern on pulmonary function study), renal involvement (persistent proteinuria >0.5 g/d, interstitial nephritis, glomerulonephritis), autoimmune hepatitis, autoimmune cytopenias (neutropenia <1500/mm^3 and/or anaemia <12 g/dl and/or thrombocytopenia <150,000/mm^3 and/or lymphopenia <1000 /mm^3) and neurological involvement (polyneuropathy, mononeuropathy, cranial pars involvement, desmyelinisation, disautonomy) radiographic or electrophysiology diagnosed or biopsy proven. We also scored the Disease Damage Index Score (SSDDI) (9) and the cumulative ESSDAI score (10) at the last follow-up.

We assessed the use of glucocorticoids (prednisone (PDN) and methylprednisolone) and the following immunosuppressors: methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), antimalarials (hydroxychloroquine and cloroquine) and cyclophosphamide (CTX). A single rheumatologist attributed the main indication(s) as well as the cause of withdrawal (lack of effectiveness, improvement, patient's own decision, and toxicity) of each drug based on the medical chart. Toxicity was considered based on laboratory assessment, rheumatologic, ophthalmologic and other subspecialist medical notes from the charts.

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

Table I. Demographic and clinical characteristics of patients with pSS according to the use of immunosuppressors and/or glucocorticoids status.

Feature	Without use of immunosuppressors and/or glucocorticoids (n=51)	Use of immunosuppressors and/or glucocorticoids (n=104)	*p*-value
Age in years	58.1 ± 13.8	57 ± 15.1	0.64
Disease duration in years	13 ± 9.3	13.4 ± 10	0.83
Female, n (%)	48 (94)	95 (91.3)	0.75
Ocular symptoms, n (%)	50 (98)	102 (98)	1
Oral symptoms, n (%)	47 (92.2)	98 (94.2)	0.73
Keratoconjuntivitis sicca, n (%)	24 (47)	44 (42.3)	0.36
NSWSF*<0.1 ml/min,%	33 (64.7)	68 (65.3)	0.33
Parotid enlargement, n (%)	19 (37.3)	58 (55.8)	0.04
Arthritis, n (%)	5 (9.8)	47 (45.2)	0.0001
Adenopathy, n (%)	7 (13.7)	36 (34.6)	0.007
Autoimmune cytopenias, n (%)	13 (25.5)	46 (44.2)	0.03
Autoimmune hepatitis, n (%)	0	10 (9.6)	0.02
Cutaneous vasculitis, n (%)	3 (5.9)	13 (12.5)	0.26
Lung interstitial disease, n (%)	0	5 (4.8)	0.17
Proteinuria, n (%)	2 (3.9)	10 (9.6)	0.21
Neurologic involvement, n (%)	11 (21.6)	36 (34.6)	0.13
Positive antinuclear antibodies, n (%)	34/48 (70.8)	68/95 (71.6)	0.84
Positive anti-Ro/ SSA antibodies, n (%)	40 (78.4)	92/102 (90.2)	0.07
Positive anti-La/ SSB antibodies, n (%)	25 (49)	60/103 (58.3)	0.3
Rheumatoid factor, n (%)	30/47 (63.8)	77/100 (77)	0.13
Low C3 levels, n (%)	2/34 (5.9)	7/86 (8.1)	1
Low C4 levels, n (%)	5/33 (15.2)	21/86 (24.4)	0.36
Median SSDDI score	3 (0-8)	2 (0-8)	0.90
Median cumulative ESSDAI score	5 (0-26)	11.5 (0-45)	0.0001
Comorbidities, n (%)			
Hypertension	20 (19.2)	8 (15.7)	0.31
Diabetes Mellitus	7 (6.7)	4 (7.8)	0.34
Dyslipidaemia	7 (6.7)	7 (13.7)	0.12

*NSWSF: Unstimulated whole salivary flow.

Results

We studied 155 patients, 92.2% females, mean age 57.4±14.7 years and median follow-up 11 (0.5-47.9) years. Overall 145 (93.5%) patients had oral symptoms, 152 (98%) ocular symptoms, 77 (49.6%) parotid enlargement, 86.2% (132/153) positive anti-Ro/SSA and 55.1% (85/154) anti-La/SSB antibodies. One hundred and twenty six patients (81.2%) had at least an extraglandular feature (median 1, range 0–7). During follow-up, 104 patients (67%) received treatment with glucocorticoids and/or inmmunosuppressors: 4 (3.8%) only glucocorticoids, 49 (47.1%) exclusively immunosuppressors and 51 (49%) their combination. The demographic and clinical characteristics of the patients according to treatment status are depicted in Table I. Overall, patients who did receive glucocorticoids and/or immunosuppressors had more frequently parotid enlargement, lymphadenopathy, arthritis, autoimmune cytopenias, autoimmune hepatitis and a higher median cumulative ESSDAI score. We did not find any differences regarding age, disease duration and damage accrual among groups. Furthermore, there was no difference in the presence of comorbidities (hypertension, diabetes mellitus and dyslipidaemia) nor in the prevalence of serological features among groups (Table I). At the logistic regression analysis, the variables that remained associated with the use of glucocorticoids and/or immunosuppressors was the presence of non-erosive arthritis OR 5.02 (95% CI 1.74–14.47, p=0.003) and the cumulative ESSDAI score OR 1.10 (95% CI 1.03–1.17, p=0.002).

As a sensitivity analysis, when we compared the group with (n=55) and without use of glucocorticoids, the first one had more arthritis (53.4% *vs*. 22.2%,

Table II. Use of glucocorticoids and immunosuppressors.

Drug	Current and/or former use n (%)	Median number of used periods	Maximum dose (range)	Toxicity
Prednisone	57 (36.7)	1 (1-5)	60 mg/day (50-100)	Not evaluated
Methylprednisolone	7 (4)	6 pulses (3-11)	1 gr/pulse	0
Methotrexate	28 (18)	1 (1-2)	12.5 mg/week (7.5-20)	4 (14.2%)
Azathioprine	37 (23.8)	1 (1-3)	100 mg/day (50-150)	5 (13.5%)
Antimalarials	72 (46.4)	1 (1-4)	Hydroxycloroquine 200mg/day (200-400) Cloroquine 150 mg/day (150-300 mg)	7 (9.7%)
Cyclophosphamide	13 (8)	6 pulses (1-8)	1 gr per dose	1 (7.6%)
Mycophenolate mofetil	2 (1)	1	2.5 mg/day (1.5-2.5)	0

Table III. Reasons for withdrawal of immunosuppressors.

Cause	MTX** former users n=18	AZA§ former users n=18	Antimalarials former users n=38	CTX¶ former users n=13	MMF¥ former users n=1
Lack of efficacy	1 (5%)	4 (22.2%)	3 (7.8%)	1 (7.6%)	1 (100%)
Improvement	8 (44.4%)	4 (22.2%)	8 (21%)	11 (84.6%)	0
Patient's own decision	5 (27.7%)	5 (27.7%)	20 (52.6%)	1 (7.6%)	0
Toxicity	4 (22.2%)	5 (27.7%)	7 (18.4%)	0	0

**MTX: methotrexate. §AZA: azathioprine. ¶CTX: Cyclophosphamide. ¥MMF: mycophenolate mofetil.

Table IV. Use of glucocorticoids and immunosuppressors in other cohorts.

Author	Country	Year	n.	Drug	Frequency (%)
Fauchais, *et al*. (15)	France	2010	445	Glucocorticoids Hydroxychloroquine Immunosuppressors	171 (38) 136 (30) 83 (19)
Baldini, *et al*. (19)	Italy	2013	495	Antimalarials	205 (40.8)
Juarez, *et al*. (16)	United Kingdom	2014	200	Glucocorticoids Antimalarials	15 (0.07) 73 (36.5)
Baldini, *et al*. (17)	Italy	2014	1115	Glucocorticoids Immunosuppressors	438 (39.2) 173 (15.5)
Migkos, *et al*. (18)	Greece	2014	806	Antimalarials	103 (12.7)
Gheitasi, *et al*. (7)	Spain	2015	1120	Hydroxychloroquine Glucocorticoids Immunosuppressors Hydroxychloroquine	282 (25.2) 475 (42.4) 148 (13) 282 (25.2)

p=0.0001) and neurological involvement (44.6% *vs*. 22.5%, *p*=0.006) and a higher median cumulative ESSDAI score (16.5 *vs*. 7, *p*=0.0001). In the logistic regression analysis the variables arthritis (OR 2.7 95% CI 1.28–5.9, *p*=0.009) and cumulative ESSDAI (OR 1.08 95% CI 1.03–1.13, *p*=0.0001) also remained associated.

Similarly when we analysed the group who received immunosuppressors (n=100 alone or in combination) *vs*. patients who did not, patients in the former group had more frequently parotid enlargement (56% *vs*. 38%, *p*=0.03), arthritis (46% *vs*. 10.9%, *p*=0.0001), neurologic involvement (36% *vs*. 2%, *p*=0.03), autoimmune cytopenias (45% *vs*. 25.4%, *p*=0.01) and also a higher median cumulative ESSDAI score (11.5 *vs*. 5, *p*=0.0001). In the multivariate analysis, again the presence of arthritis (OR 4.73, 95% CI 1.78–12.5, *p*=0.002) and the cumulative ESSDAI score (OR 1.09, 95% CI 1.03–1.15, *p*=0.002) remained associated.

The percentage of use, median of use periods, maximum dose and main indications of steroids and immunosuppressive therapy are shown at Table II. The drugs most frequently used were antimalarials (46.4%, n=72) followed by PDN (36.7%, n=57), AZA (23.8%, n=37) and MTX (18%, n=28). Only 8% (n=13) received CTX and 1% (n=2) MMF. In addition 7 patients (4%) received pulses of methylprednisolone. Furthermore, only three patients received rituximab but in the context of chemotherapy for lymphoma treatment. Among the group of patients who received glucocorticoids, the main indication was the combination of diverse extraglandular features during the follow-up (skin vasculitis, parotid enlargement, arthritis, etc.), being the median dose 10 mg. The maximal dose was 60 mg/day (50–100), deserved for severe features. Methylprednisolone was used in neurologic involvement. As expected, antimalarials and MTX were mostly used for arthritis, AZA for autoimmune hepatitis and cyclophosphamide was employed for neurological involvement. We had a low prevalence of interstitial pneumonitis, and all of these cases were managed with azathioprine. Two patients received MMF, being the indication vasculitis.

Only 17 patients (10.9%) out of the 155 patients received glucocorticoids and/or immunosuppressors specifically for the presence of sicca symptoms (excluding parotid enlargement): 3 prednisone, 1 methotrexate, 1 azathioprine and 12 antimalarials.

Table III shows the causes of withdrawal of immunosuppressors. Among 88 patients former users of MTX, AZA, antimalarials, CTX and MMF, 39% (n=35) discontinued treatment due to improvement, 35.2% (n=31) due to patient's own decision, 18.1% (n=16) due to toxicity and 11% (n=10) due to lack of effectiveness. However among the patients who suspended antimalarials, half of them suspended due to their own decision. We found toxicity in 14.2% of MTX users, 13.5% of AZA, 9.7% antimalarials and 7.6% for CTX (Table II). Of the 4 patients with MTX toxicity, 1 had leucopenia, 2 gastrointestinal symptoms and 1 weigh loss. Among the AZA toxicity cases, four had gastrointestinal symptoms and 1 leucopenia; whereas the cases of antimalarials toxicity were due to gastrointestinal symptoms (n=4), skin hyperpigmentation (n=1) and ophthalmologic deposits (n=3). The patient who had CTX toxicity developed secondary amenorrhoea. We were not able

to evaluate prednisone toxicity due to lack of information.

Discussion

The main treatment in pSS is focused on the management of oral and ocular symptoms (1). On the other hand, the spectrum of SS also encompasses the presence of extraglandular features, as patients may develop a large number of them either at onset or during their follow-up conferring a poor prognosis (11). However the management of systemic involvement using AZA, CTX, MTX, MMF, antimalarials and glucocorticoids is mainly based on case-series, open-label studies and expert opinion (1, 2, 12-14).

Recently a study evaluated the use of glucocorticoids and immunosuppressors for systemic features in pSS. In this multicentre Spanish cohort, 25% patients were treated with antimalarials, 42% with steroids and 13% with immunosuppressors (7). Table IV depicts the use of immunosuppressors and glucocorticoids among other cohorts (7, 15-19). In comparison with these cohorts, we found a higher use of antimalarials and immunosuppressors, but a similar figure for glucocorticoids with the exception of one study (16). However it is important to highlight that we evaluated the use of these drugs, for both glandular and extraglandular features, an issue that could impact the results.

In a Spanish population, the variables associated with the use of immunosuppressor treatment were a higher basal ESSDAI score, neutropenia and rheumatoid factor (7). Conversely, in our cohort, we identified the presence of non-erosive arthritis and a higher cumulative ESSDAI score as associated factors.

Although immunossupressors are commonly used in pSS (1), there is a lack of information regarding their safety and cause of withdrawal, and most of the time, data regarding this topic is extrapolated from other autoimmune diseases. Here we identified that the main reasons for stopping immunosuppressors were improvement, followed by patient's own decision; whereas the prevalence of toxicity was moderate (18%).

Regarding MTX, we found toxicity in 22.2% of our patients, a similar figure (16%) as reported in rheumatoid arthritis (RA) where in only 2.3% is severe (19); being the main causes abnormal liver function tests, alopecia, oral ulcers and gastrointestinal symptoms. On the other hand, 27.7% of the patients had toxicity to AZA and 22.2% lack of effectiveness. In contrast in patients with SLE, the main reasons to suspend the drug included de-escalation (21%), treatment failure (18%) and toxicity (4%) (20). Moreover among lupus patients, CTX has been related to ovary dysfunction and higher incidence of infections in comparison to MMF and azathioprine (21). In the present study, only 13 of our patients used this drug, achieving improvement in most of them and we found toxicity in 7.6%. We used MMF in only 2 patients, one with lack of effectiveness. A previous study of 11 patients with pSS showed interruption of this drug because of 1 episode of infection, 2 episodes of vertigo and 4 patients with gastrointestinal complaints (21).

By far, the most used drug was antimalarials as almost half of our patients received it. This result is in agreement with an Italian population, where 40.8% were under this treatment (22). Nevertheless, a lower use has been observed in Spanish (7) and Greek patients (18). Currently antimalarials are recommended for articular involvement associated with pSS (1, 6), that was the main indication in our cohort. Interestingly, we found that the main cause of withdrawal of this drug was the patient's own decision. We could speculate that this condition might be attributed to several factors including lack of effectiveness, impaired tolerance or inclusive costs. In addition we found toxicity in 18.4% of the patients. Among an Italian cohort of 202 patients with pSS under antimalarials; the incidence rate of global discontinuation of this treatment was 6.34 per 1,000 patient-year. Reasons for discontinuation were: lack of efficacy in 11%, adverse events in 35.8%, non-compliance 41% and miscellaneous causes such as surgery/comorbidities and concomitant medications in 13%. Indeed adverse events were mostly related to non-ophthalmologic reasons such as skin rash and gastrointestinal symptoms. Moreover, when timing of HCQ withdrawal was separately considered, discontinuation due to adverse events occurred after 4.4±5.9 months of treatment; whereas discontinuation due to lack of efficacy and to non-compliance were documented significantly later over the follow-up (23).

Finally, the use of immunosuppressors as well as steroids has shown limited benefits for sicca features based on the available literature (7). Nevertheless, we identified 17 patients (9.1%) who received glucocorticoids and/or immunosuppressors only for treating sicca symptoms.

Moreover, in the Spanish cohort, the authors found an inadequate use of immunosuppressors in 14% of the patients mainly associated with articular involvement of low/moderate activity; and in 7% for glucocorticoids at a dose >20 mg/day (7).

As a limitation of our study, due to its retrospective design, we were not able to evaluate toxicity regarding glucocorticoids. However, we believe that our study adds information to the current literature.

In conclusion, more than 50% of pSS patients received glucocorticoids and/or immunosuppressors. Causes of withdrawal included improvement but also a not a negligible number of patients suspended them by own decision and toxicity, alerting physicians of secondary adverse events and tolerability with the use of this treatment.

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