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How are we treating our systemic patients with primary Sjögren syndrome? Analysis of 1120 patients☆

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ABSTRACT

Objective: To describe how systemic disease is treated in a large cohort of Spanish patients with primary Sjögren syndrome (pSS) in daily practice, focusing on the adequacy of therapies for the level of systemic activity measured by ESSDAI score.

Patients and methods: By December 2014, our database included 1120 consecutive patients who fulfilled the 2002 classification criteria for SS. Therapeutic schedules were classified into 4 categories: no systemic therapies, hydroxychloroquine (HCQ) and/or low dose glucocorticoids (GCS) (<20 mg/day), high dose GCS (>20 mg/day) and use of second-line therapies (immunosuppressive agents, intravenous immunoglobulins [IVIG] and/or rituximab [RTX]).

Results: There were 1048 (94%) women and 72 (6%) men , with a mean age at diagnosis of 54 years. The main drug-based therapeutic approaches for systemic pSS during follow-up were HCQ in 282 (25%) patients, GCS in 475 (42%, at doses >20 mg/day in 255—23%), immunosuppressive agents in 148 (13%), IVIG in 25 (2%) and RTX in 35 (3%) patients. HCQ was associated with a lower risk of death (adjusted HR of 0.57, 95% 0.34–0.95). We classified 16 (7%) of the 255 patients treated with >20 mg GCS and 21/148 (14%) treated with immunosuppressive agents as patients inadequately treated, mainly associated with articular involvement of low/moderate activity.

Conclusion: The management of pSS should be organ-specific, using low dose GCS in patients with moderate systemic activity, limiting the use of high dose GCS and second-line therapies to refractory or potentially severe scenarios. The use of systemic therapies for dryness, chronic pain or fatigue is not warranted.

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1. Introduction

Sjögren syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands, causing dryness of the main mucosal surface, such as the mouth, eyes, nose, pharynx, larynx and vagina [1]. However, the clinical spectrum of SS extends from dryness to systemic involvement (extraglandular manifestations) and may include a large number of manifestations. The disease overwhelmingly affects middle-aged women, but may also affect children, men and the elderly. SS may be a severe disease with excess mortality, mainly related to systemic involvement and lymphoma, and is expressed in many guises, depending on the specific epidemiologic, clinical, or immunologic features [2].

The therapeutic management of SS is principally centered on control of the main symptoms, sicca features, using substitutive and oral muscarinic agents [3]. However, systemic involvement clearly marks the disease prognosis. The development of the EULAR-SS disease activity index (ESSDAI) [4] by the EULAR task force on SS is a step forward in the evaluation of patients with systemic Sjögren, who should receive a closer follow-up and more robust therapeutic management [5]. As a rule, the management of systemic Sjögren should be organ-specific, with glucocorticoids and immunosuppressive/biological agents limited to potentially-severe scenarios. However, a systematic review highlighted the limited evidence available for the drugs most frequently used in primary SS and the difficulties of offering solid therapeutic recommendations [6]. In this scenario, information about how these complex patients are treated in a real life setting may be very useful.

The aim of this study was to describe how systemic Sjögren is treated in a large cohort of Spanish patients with primary SS in daily practice, focusing on the adequacy of drug therapies for the level of systemic activity measured by the ESSDAI score.

2. Patients and methods

2.1. Patients

The GEAS-SS Study Group was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included 21 Spanish centers with substantial experience in the management of patients with systemic autoimmune diseases. Both incident and prevalent cases were included; for incident cases, the diagnosis of primary SS was made during the first study visit after January 2005, while for the prevalent cases, the diagnosis was established before January 2005. By December 2014, the database included 1120 consecutive patients (686 prevalent cases) who fulfilled the 2002 classification criteria for pSS [7]. Exclusion criteria were chronic HCV/HIV infection, previous lymphoproliferative processes and associated systemic autoimmune diseases. Diagnostic tests for SS (ocular tests, parotid scintigraphy and salivary gland biopsy) were performed according to the European Community Study Group recommendations [7].

2.2. Definition of variables

The date of disease diagnosis was defined as the date when the physician responsible for the patient's follow-up confirmed fulfillment of the 2002 criteria [7]. Systemic involvement was defined according to the ESSDAI [4], which evaluates 12 domains or organ systems. Each domain is divided into 3–4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity). The ESSDAI score at diagnosis was retrospectively calculated by examination of medical records in order to collect disease activity before the date of SS diagnosis. Disease activity states (DAS) were defined according to the baseline ESSDAI score (low DAS for an ESSDAI <4, moderate DAS for an ESSDAI between 5 and 13, and high DAS for an ESSDAI >13) [8]. Therapeutic schedules were classified into 4 categories: no systemic therapies, HCQ and/or low dose of GCS (<20 mg/day), high dose of GCS (>20 mg/day) and use of second-line therapies (immunosuppressive agents, IVIG and/or RTX). According to the systemic definitions included in the ESSDAI, we defined the use of GCS (>20 mg/day) in patients with an ESSDAI score < 4 (equivalent to moderate arthritis, defined as 1–5 affected joints) and the use of second-line therapies in patients with an ESSDAI score <6 (equivalent to severe arthritis, moderate vasculitis or severe cytopenia) as inadequate therapeutic regimens.

2.3. Statistical analysis

Descriptive data are presented as means and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Systemic therapies were categorized as never or ever used during the follow-up, and included the use of HCQ, oral GCS (higher or lower than 20 mg/day), immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate and methotrexate), IVIG and RTX. The clinical and immunological characteristics and presence/level of activity recorded in the ESSDAI organ domains were assessed at diagnosis. To compare the main baseline features of patients according to the use or not of systemic therapies *t*-test or chi-square tests were used. Logistic multivariate regression model was constructed to analyze independent factors associated with the use or not of systemic therapies. Variables with a p-value < 0.1 in the univariate analysis were included in the model and stepwise model selection by Akaike information criterion (AIC) was used. Cox proportional-hazards regression analysis allowed adjustment for age at diagnosis, gender and level of ESSDAI activity as confounders, in order to establish independent systemic therapy variables associated with the outcomes evaluated such as lymphoma, death or a combination of both. The hazard ratios (HR) and their 95% confidence intervals (CI) obtained in the adjusted regression analysis were calculated. All significance tests were 2-tailed and values of $p < 0.05$ were considered significant. All analyses were conducted using the R version 3.0.3 for Windows statistical software package.

3. Results

3.1. Baseline characterization

Baseline characteristics are summarized in Table 1. The cohort consisted of 1120 patients, including 1048 (94%) women and 72 (6%) men (female: male ratio, 15:1), with a mean age at diagnosis of 54.45 ± 15.21 years (range, 14–90). At diagnosis, 1065 (95%) patients presented dry mouth, 1062 (95%) dry eye, 955/1042 (92%) had altered ocular diagnostic tests (Schirmer's test and/or corneal stainings), 731/841 (87%) altered parotid scintigraphy and 485/557 (87%) a salivary gland biopsy showing focal lymphocytic infiltration. The main immunologic features at diagnosis were ANA >1/80 in 1004/1118 (90%) patients, anti-Ro/SS-A in 823/1116 (74%), RF in 566/1083 (52%), anti-La/SS-B in 508/1113 (46%), low C4 levels in 127/1057 (12%), cryoglobulinemia in 81/652 (12%) patients, low C3 levels in 105/1058 (10%) and monoclonal gammopathy in 88/879 (10%). The mean total ESSDAI score at diagnosis was 5.91 ± 6.77.

3.2. Systemic therapeutic approaches and baseline features

The main drug-based therapeutic approaches for systemic Sjögren ever used during the follow-up were HCQ in 282 (25%) patients, GCS in 475 (42%, used at doses > 20 mg/day in 255—23%), immunosuppressive agents in 148 (13%), IVIG in 25 (2%) and RTX in 35 (3%) patients. According to therapeutic schedules, 634 (57%) patients were untreated, 183 (16%) were treated with HCQ and/or low dose of GCS, 132 (12%) with high doses of GCS and the remaining 170 (15%) with the addition of immunosuppressive agents, IVIG and/or rituximab. Table 2 compares the main baseline features of patients according to the use or not of systemic therapies. The use of systemic therapies