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Arthritis in primary Sjögren's syndrome: Characteristics, outcome and treatment from French multicenter retrospective study

Adrien Mirouse[a,b], Raphaèle Seror[c], Eric Vicaut[d], Xavier Mariette[c], Maxime Dougados[e], Anne-Laure Fauchais[f], Alban Deroux[g], Azeddine Dellal[h], Nathalie Costedoat-Chalumeau[i,j,k], Guillaume Denis[l], Jérémie Sellam[b,m], Jean-Benoît Arlet[n], Christian Lavigne[o], Geoffrey Urbanski[o], Dominique Fischer-Dumont[p], Abdou Diallo[d], Olivier Fain[a,b], Arsène Mékinian[a,b,*], on behalf of Club Rhumatismes Inflammation and SNFMI

[a] Service de médecine interne, Hôpital Saint-Antoine, APHP, Paris, France
[b] Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine (CRSA), F-75012 Paris, France
[c] Service de rhumatologie, Hôpital du Kremlin-Bicêtre, APHP, Bicêtre, France
[d] Service de biostatistiques médicales, Hôpital Lariboisière, APHP, France
[e] Service de rhumatologie B, Hôpital Cochin, Paris, France
[f] Service de médecine interne, CHU de Limoges, Limoges, France
[g] Service de médecine interne, CHU Grenoble, La Tronche, France
[h] Service de rhumatologie, Hôpital Montfermeil, Montfermeil, France
[i] Service de médecine interne, centre de référence maladies auto-immunes et systémiques rares, Hôpital Cochin, APHP, Paris, France
[j] Université Paris Descartes-Sorbonne Paris Cité, Paris, France
[k] INSERM U 1153, Center for Epidemiology and Statistics Sorbonne Paris Cité (CRESS), Paris, France
[l] Service de médecine interne, Hôpital de Rochefort, France
[m] Service de rhumatologie, Hôpital Saint-Antoine, APHP, Paris, France
[n] Service de médecine interne, Hôpital Européen Georges Pompidou, APHP, Paris, France
[o] Service de médecine interne, CHU Angers, Angers, France
[p] Service de rhumatologie, Hôpital Avicenne, APHP, Bobigny, France

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ABSTRACT

Objective: To describe the characteristics and the outcome of primary Sjögren Syndrome (pSS) associated arthritis and to compare the efficacy of different therapeutic regimen.

Methods: We conducted a retrospective study using Club Rhumatisme and Inflammation (CRI) and French Internal Medicine Society (SNFMI) networks. All patients with a diagnosis of pSS and at least one episode of clinical and/or echographic synovitis were included. Patients with synovitis (cases) were compared to pSS patients without synovitis (controls).

Results: 57 patients (93% women) were included with a median age of 54 years [45–63]. Patients with synovitis had more frequently lymph node enlargement (12.3% vs. 1.8%, p = .007) and a higher ESSDAI score (8 [6–12] vs. 2 [1–4], p < .0001). There was no difference concerning CRP levels, rheumatoid factor and cyclic citrullinated peptide (CCP)-antibodies positivity. Among 57 patients with synovitis, 101 various treatment courses have been used during the follow-up of 40 [22.5–77] months. First treatment course consisted in steroids alone (3.5%), steroids in association (79%) with hydroxychloroquine (HCQ) (49%), methotrexate (MTX) (35%), rituximab (RTX) (5.3%) or other immunosuppressive drugs (7%). HCQ, MTX, and RTX were associated with a significant reduction of tender and swollen joint count, and a significant steroids-sparing effect. No difference could be shown for the joint response between these treatment regimens.

Conclusion: pSS articular manifestations may include synovitis which could mimic rheumatoid arthritis but differ by the absence of structural damage. Even if the use of HCQ, MTX, and RTX seem to be effective for joint involvement, the best regimen remains to be determined.

* Corresponding author.
E-mail address: arsene.mekinian@aphp.fr (A. Mékinian).

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1. Introduction

Primary Sjogren's syndrome (pSS) is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland functions. The histological hallmark is a focal lymphocytic infiltration of the salivary gland, and the spectrum of the disease may extend to a systemic process with vasculitis and diverse extra-glandular systemic manifestations. Beside the glandular disease, joint involvement is reported in 20 to 60% of pSS patients, and among them one third of patients present synovitis [1–3]. Despite the presence of CCP-antibodies in 5 to 10% of pSS, But there is usually no joint erosion during the course of pSS [4–6]. However, in at least half of these cases with CCP-antibodies, there was an evolution toward rheumatoid arthritis (RA) [7].

Arthralgia and synovitis have been described as associated with other pSS inflammatory manifestations like recurrent parotid gland enlargement, cutaneous vasculitis, or cryoglobulinemia [8–10]. Few studies reported the efficacy of various treatments for joint involvement, and there is a lack of data concerning therapeutic management of pSS-associated synovitis. Hydroxychloroquine (HCQ) and methotrexate (MTX) efficacy has been reported in patients with pSS and joint involvement but, among them, only 35% have clinical synovitis [2]. Another study including 19 patients with joint involvement showed no efficacy of HCQ [11]. Biological-targeted therapies, including TNFα inhibitors and rituximab (RTX), have been studied in pSS and failed to improve glandular symptoms and constitutional signs [12–17]. However, RTX could improve some extraglandular systemic features, like neurological involvement and joint pain, but no studies focused on pSS-associated inflammatory arthritis [18].

The aims of our study were to describe the characteristics and the outcome of pSS-associated arthritis and to compare the efficacy of different therapeutic regimen, like HCQ, MTX and RTX.

2. Patients and methods

We conducted a multicentric retrospective study using the “French Inflammatory Joint Disease Working Group” (Club Rhumatismes et Inflammation) and the “French Internal Medicine Society” (SNFMI) networks. All physicians were asked to fulfill charts. This study was conducted in compliance with the protocol of Good Clinical Practices and Declaration of Helsinki principles. In accordance with French law, formal approval from an ethical committee was not required for this observational retrospective study.

2.1. Inclusion criteria

All patients (≥18 years) with a diagnosis of primary Sjögren-Syndrome (pSS) (American-European Consensus Group-AECG criteria) and at least one episode of clinical and/or ultrasound synovitis during the follow-up were included among 13 French Internal Medicine and Rheumatology departments [19]. Patients were identified from hospital databases using code M35.0, M35.09 and M65.4 from the International Classification of Diseases (ICD-10). Patients with other diagnosis of inflammatory (*p.e* ACR-EULAR criteria for rheumatoid arthritis) [20], infectious or microcrystalline arthritis (gout, chondrocalcinosis) were excluded. All patients' medical records were reviewed by 2 investigators (A Mirouse and A Mekinian).

2.2. Data collection

Following data were recorded from patients' medical charts: age, sex, diagnosis date, presence of ocular and oral subjective and objective symptoms, extra-articular signs including constitutional manifestations, lymphadenopathy, glandular involvement, cutaneous, pulmonary, renal, muscular, and neurological manifestations. Articular manifestations included the number of tender and swollen joints, type of joints involved and the presence of morning stiffness. Synovitis was diagnosed with clinical examination and/or with joint ultrasonography. Articular and other pSS manifestations were collected at the diagnosis, at each therapeutic course initiation, and the last available visit. Disease activity was assessed using EULAR Sjögren Syndrome Disease Activity Index (ESSDAI), at the inclusion and during the follow-up [21].

Biological data were recorded at the diagnosis, including complete blood cell count, immunological tests (Anti-Nuclear Antibodies [ANA], Extractable Nuclear Antibodies [ENA] Rheumatoid Factor [RF], CCP-antibodies, complement and cryoglobulinemia). C-reactive protein (CRP) levels were collected at the inclusion and during the follow-up. Radiological findings were recorded, especially the presence of erosions.

Indication for treatment initiation was recorded and defined as either for articular manifestations or other pSS manifestations. All therapeutic courses were recorded, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), steroids, HCQ, MTX, RTX and other disease-modifying antirheumatic drugs (DMARDs) and biological-targeted treatments. Steroids dose was collected at the inclusion and during the follow-up.

A control group of pSS patients without any synovitis was selected from participating centers to determine the factors associated with joint involvement. Two controls were included for each pSS patient with arthritis and matched for age (± 10 years), gender and pSS disease duration.

Treatment response was assessed for each treatment course. Complete treatment response was defined for joint involvement as disappearance of all arthralgia and synovitis. Partial response was defined as improvement of > 50% of the swollen joint count (i.e. number of synovitis) and non-response in remaining cases. ESSDAI scale and C-reactive protein levels were also assessed before and at the end of each treatment regimen. Reasons for treatment interruption were collected and defined as remission, inefficacity, relapse or adverse side effect.

2.3. Statistical analysis

Data are expressed as medians with interquartiles range and numbers with frequencies. To compare the quantitative values, *t*-test or Wilcoxon -Mann Whitney tests were used as appropriate. To compare qualitative values, chi-square tests or Fisher's exact tests were used for parametrical and non-parametrical values, respectively. To assess the efficacy of each treatment, all patients' treatment courses were analyzed and used to compare the efficacy of various drugs.

Taking into account the fact that patients may have successively different treatments and that the effect of treatment can be related to its line, we compared the changes in parameters among HCQ, MTX, or RTX treatment by ANOVA for repeated measurements with baseline covariables and line of treatment forced in the model. Parametric or non parametric method was used according to the statistitical distribution of the variable. For binary variables we used a general estimating equations (GEE) binomial model with an Andersen-Gill approach.

All analyses were done using R software version 3.0.2 (R Core Team 2015) and p value < .05 was considered as significant.

3. Results

3.1. pSS patients with synovitis

During the study period, 57 patients (93% women) were included with a median age at pSS related synovitis diagnosis of 54 years [45–63] (Table 1). Subjective xerophtalmia and xerostomia were noted in 54 (94%) and 55 (97%), respectively. A focus score of ≥1 foci/4 mm^2 was present at salivary gland biopsy for 44 (78.6%) patients. All (100%) patients had at least one episode of clinical synovitis. Twenty-nine (51%) patients had a joint evaluation with ultrasound (n = 23) or Magnetic Resonance Imagery (MRI) (n = 6) which confirmed clinical

Table 1
Characteristics of pSS patients with or without synovitis.

	Joints involvement with synovitis	Without synovitis	p
	N = 57	N = 114	
Diagnosis age (years) median[IQR]	54 [23–81]	55 [18–81]	0.05
Sex, man n (%)	4 (7.0%)	4 (3.5%)	0.4
Disease duration (months) median[IQR]	8 [4–23]	10 [5–26.8]	0.47
Xerophtalmia			
Subjective n (%)	54 (94.7%)	101 (88.6%)	0.3
Objective n (%)	34 (60.7%)	101 (88.6%)	< 0.0001
Xerostomia			
Subjective n (%)	55 (96.5%)	107 (93.4%)	0.4
Objective n (%)	24 (42.9%)	108 (94.7%)	< 0.0001
Focus score of ≥1 foci/4 mm^2	44 (78.6%)	88 (77.9%)	0.4
Parotid gland enlargement n (%)	9 (15.8%)	41 (40.0%)	0.007
Joint pain n (%)	57 (100%)	83 (73%)	< 0.0001
Synovitis number median[IQR]	4 (2–6)	-	
Skin n (%)	12 (21.2%)	34 (29.8%)	0.3
Kidney n (%)	1 (1.8%)	0	0.4
Lung involvement n (%)	6 (10.5%)	3 (2.6%)	0.06
Peripheral nervous system involvement n (%)	7 (12.3%)	7 (6.1%)	0.2
Central neurological involvement n (%)	1 (1.8%)	1 (0.9%)	0.3
Myositis n (%)	1 (1.8%)	2 (1.8%)	0.2
Lymphadenopathy, n (%)	7 (12.3%)	2 (1.8%)	0.007
Lymphoma, n (%)	1 (1.8%)	0	0.3
Hemoglobin (g/dl) median[IQR]	13 [11.8–13.5]	13.1 [11.9–14.3]	0.2
Platelets (G/l) median[IQR]	239 [205–280]	266 [228.5–317.5]	0.2
Neutrophils (G/l) median[IQR]	4.2 [2,9–5.3]	2.96 [2.24–3.81]	0.002
Lymphocytes (G/l)median[IQR]	1.9 [0.9–2.3]	1.54 [1.27–2.01]	0.2
Gammaglobulins (g/l) median[IQR]	14 [12–18.8]	14 [10.8–17.1]	0.5
Monoclonal gammapathy, n (%)	1 (2.1%)	6 (5.3%)	0.4
ESR (mm per hour), median[IQR]	19 [11.5–35]	18 [9.5–28.5]	0.2
CRP (mg/l) (N < 5) median[IQR]	5 [3–9.25]	5 [5–6]	0.06
ANA median[IQR]	640 [160 1280]	640 [0–1280]	0.7
SSa n (%)	42 (77.8%)	81 (71%)	
SSb n (%)	19 (36.5%)	45 (39.4%)	
C3 (mg/l) median[IQR]	1.02 [0.86–1.19]	1.07 [0.96–1.25]	0.4
C4 (mg/l) median[IQR]	0.24 [0.12–0.32]	0.21 [0.17–0.26]	0.4
Cryoglobulinemia n (%)	3 (5.3%)	1 (0.9%)	0.1
RF n (%)	22 (44.9%)	36 (31.9%)	0.4
CCP-antibodies n (%)	6 (10.5%)	3 (2.7%)	0.06
β2-microglobulin (mg/l) median[IQR]	3.03 [1.99–3.92]	2.12 [1.77–2.61]	0.06
ESSDAI, median (IQR)	8 [6–12]	2 [1–4]	< 0.0001
NSAID n (%)	12 (21%)	22 (19%)	0.8
Methotrexate n (%)	21 (37%)	1 (0.08%)	< 0.0001
Steroids (%) / amount (mg/day) median[IQR]	43 (75%) / 10 [9.4–15]	7 (6%)/ -	< 0.0001
Hydroxychloroquine n (%)	38 (67%)	17 (15%)	< 0.0001

Values are medians with interquartiles and numbers with frequencies.
Abbreviations: ANA: Anti-Nuclear Antibodies, CCP: Cyclic Citrullinated Petpide, CRP: C-reactive Protein, ESR: Erythrocyte Sedimentation Rate, ESSDAI: EULAR Sjögren Syndrome Disease Activity Index, NSAID: Non-steroidal anti-inflammatory drugs, RF: Rheumatoid Factor.

synovitis for all patients. At the time of diagnosis of joint manifestations, the main pattern was a symmetric polyarthritis (n = 39, 67%), touching metacarpophalangeal joints in 36 (68%) cases and proximal interphalangeal joints in 30 (57%) cases. Median number of tender and swollen joints at the diagnosis was 8 [4–12] and 4 [2–6], respectively. Median morning stiffness was 30 [30–60] minutes and 45 (82%) patients reported night awakening. Laboratory findings showed median CRP level at 5 [3–9.3] mg/l. Beta-2-microglobulin levels were at 3.03 [1.99–3.92] mg/l. Median gammaglobulin level was 14.0 [12.0–18.8] g/l. ANA levels were at 1/640 [1/160–1/1280] with SSa and SSb specificity in 42 (78%) and 19 (37%), respectively. Twenty-two (45%) patients had rheumatoid factor positivity and 6 (10.5%) patients had CCP-antibodies positivity (median 114 [16–148] UI/l). A cryoglobulinemia was detected in 3 (5%) patients. Initial median ESSDAI score was 8 [6–12]. Sixteen (28%) patients, including all 6 patients with CCP-antibodies, had radiological evaluation at the end of follow-up (32.5 [22.5–49.8] months), and no patient had structural dammage.

3.2. Comparison of pSS with and without synovitis

During the same study period, we identified 114 pSS patients without synovitis which represent the control group and were compared to pSS patients with synovitis. pSS patients' characteristics with and without synovitis are described in Table 1. Subjective xerostomia and xerophtalmia frequencies were similar in both groups, whereas objective xerophtalmia and xerostomia and parotid gland enlargement were more frequent in patients without synovitis. Patients with synovitis had more frequently lymph nodes enlargement (12.3% vs. 1.8%, p = .007). Patients with synovitis had a significant higher ESSDAI score compared to patients without synovitis (8 [6–12] vs. 2 [1–4], p < .0001). Patients from the 2 groups did not differ regarding acute-phase reactants, nor RF positivity (Table 1). Patients with synovitis had a trend toward a higher CCP-antibodies positivity (14% vs. 2.7%, p = .06).

Regarding treatments, patients with synovitis were treated more

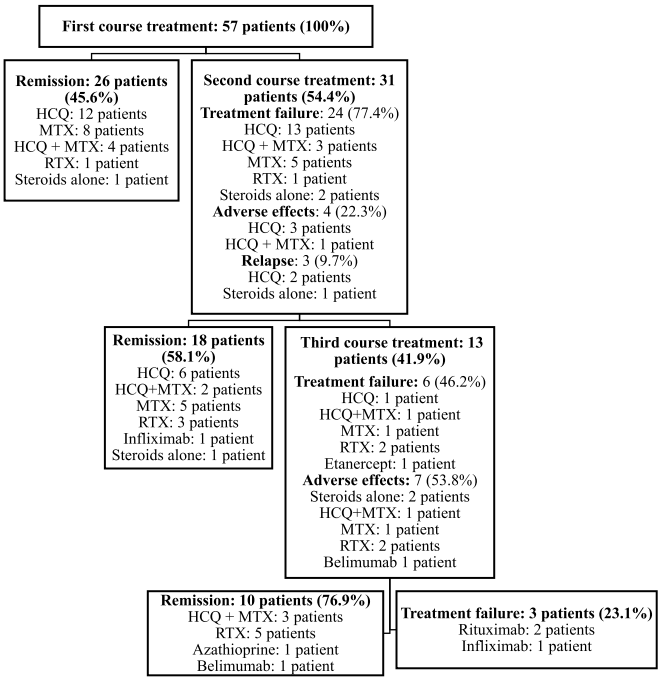

Fig. 1. Flow chart of the 101 treatment courses:Abbreviations: HCQ: Hydroxychloroquine, MTX: Methotrexate, RTX: Rituximab.

frequently with steroids (43 [75%] vs. 7 [6%], p < .0001), MTX (21 [37%] vs. 1 [0.08%], p < .0001) and HCQ (38 [67%] vs. 17 [15%], p < .0001). There was no difference concerning the frequencies of NSAID use.

3.3. Treatments of pSS with synovitis

Among 57 patients with synovitis, 101 various treatment courses have been used during the follow-up of 40 [22.5–77] months (Fig. 1). All patients received at least one therapeutic course, the first course consisted in steroids alone (3.5%), HCQ (49%), MTX (35%), RTX (5.3%) or other immunosuppressive drugs (7%). Treatment was initiated for joint involvement in 53 (93%) patients and the first-course median duration was of 4.9 [2.7–7.4] months. No clinical and biological finding did influence the first-course treatment choice. A second therapeutic course was initiated in 31 (54.4%) cases, for relapse (n = 6), treatment failure (n = 16) or adverse side effect (n = 9) and consisted in steroids alone (3%), HCQ (19%), MTX (29%), RTX (32%) or other immunosuppressive drug (16%). The second-course median duration was of 5.1 [3.6–16.6] months. Thirteen patients (22.8%) received a third course treatment for relapse (n = 3), treatment failure (n = 5) or adverse side effect (n = 5) and consisted in steroids alone (8%), MTX (23%), RTX (46%) or other immunosuppressive drug (23%). The third-course median duration was of 7 [3.3–9.7] months.

Comparison between HCQ, MTX, and RTX considering the 77 therapeutic courses including only one of these three drugs is reported in Table 2. At baseline, no significant difference was found regarding the number of tender and swollen joint counts, ESSDAI and C-reactive protein levels.

Only HCQ treatment was associated with a decrease in tender (0 [0–4] vs. 7 [3–9] at baseline; p = .0005) and swollen (0 [0–1] vs. 2 [1–5] at baseline; p < .0001) joint counts. Partial and/or complete joint response was showed in 9/20 (45%) courses of MTX, 24/38 (63%) courses of HCQ and 14/19 courses (74%) of RTX, whereas complete joint response were quite similar with 3 regimens (22% vs 32% and 21%, respectively).

Considering patients treated by MTX, HCQ or RTX, the number of complete/partial joint responses was 52% for the first course, 76% for the second course and 83% for the third course (p = .09), and the trends were similar considering each drug separately.

There was no significant difference between HCQ, MTX, and RTX concerning their effect on tender and swollen joint count, CRP level, ESSDAI score and steroids sparing effect (Table 2).

All 3 treatments (HCQ, MTX, and RTX) were associated with a significant reduction of ESSDAI score and a significant steroids-sparing effect (Table 2).

No difference has been found for the joint response between three treatment regimen (MTX vs. HCQ, OR 1.55 [0.18–13.55], p = .69; MTX vs. RTX, OR 5.08 [0.49–52.17], p = .17; HCQ vs. RTX OR 3.28 [0.28–38.02], p = .34) (Table 3).

4. Discussion

As far as we know, this is the largest study of patients with pSS-synovitis, which report clinical, biological and radiological features, outcome and treatment of 57 patients. Main presentation was a peripheral symmetric polyarthritis and patients with synovitis presented more frequently lymph node enlargement. HCQ, MTX, and RTX were associated with a significant reduction of ESSDAI score and showed similar efficacy for joint involvement. Despite frequent presence of RF and CCP-antibodies, no structural progression was observed during follow-up in patients who had an X-ray evaluation, including all patients with CCP-antibodies.

Compared with patients without articular manifestations, patients with synovitis presented more frequently lymph node enlargement, which might be a sign of B-Cell chronic activation. Patients with synovitis had also a significant higher ESSDAI score than patient without synovitis. Although synovitis is part of ESSDAI score evaluation, the difference between two groups is too important to be explained only by synovitis. Systemic manifestations in pSS have already been related to articular manifestations [2]. In our study, there was a tendency toward a higher prevalence of CCP-antibodies in patients with synovitis, as it has already been reported [1,22,5]. It could be argued that our patients with CCP-antibodies had RA with associated Sjögren's syndrome (sSS), but we found similar prevalence of RF and CCP-antibodies compared to other pSS studies and no erosions occurred during the follow-up [4,5,27].

There is no consensual treatment for pSS, especially for articular manifestations and no study specifically addressed the treatment efficacy for joint involvement with synovitis. One study reported no effect of HCQ on articular manifestations in pSS, but synovitis status was not analyzed [11]. Another double blinded controlled randomized trial showed no difference between HCQ and placebo concerning dryness, pain and fatigue and ESSDAI score, but only few patients with inflammatory joint involvement and synovitis have been included [28]. One pilot study suggested that tumor necrosis factor inhibitor (infliximab) might be beneficial, but subsequent multicenter trials did not confirm these results [12,13,29,30]. Only few patients with joint involvement have been analyzed in these studies. Some studies suggested that RTX could be efficient on pSS joint involvement [17,31]. A recent meta-analysis of RTX in pSS showed efficacy of RTX compared to placebo concerning salivary flow rate [32]. All those studies were not designed to specifically study the effect of treatment on articular manifestations and/or synovitis. In our study, HCQ, MTX and RTX were efficient to control articular manifestations, including synovitis, reduced ESSDAI score and spare steroids use. These data are in line with real-life registries of pSS, which reported significant improvement of ESSDAI, and neurological and joint involvements [16,17]. Promising data have been recently reported with BAFF inhibitor, belimumab, but only few patients with synovitis have been included in these studies and in our series the number of pSS under belimumab was too low to analyze its efficacy [33,34].

Our study has several biases which could limit definitive conclusions. First of all, it is a retrospective study and there might be some

Table 2
Comparison of joint response, ESSDAI and steroids dose at the initiation and the end of various therapeutic courses.

Characteristics	All courses	HCQ	Methotrexate	RTX	p-Value between HCQ, MTX, RTX groups (ANOVA)
	N = 101	N = 35	N = 17	N = 19	
Tender joint count	5 (1 − 10)	7 (3 − 10)	7 (4–14)	3 (0–6)	0.07
Before/at the end	1 (0–4)	0 (0–4)	4 (1–6)	1.5 (0–5.5)	
		(*= 0.0004)	(*p = .07)	(*p = .3)	
Swollen joint count	2 (1–5)	2 (1–5)	3.5 (1–4)	1 (0–3)	0.07
Before/at the end	0 (0–1.2)	0 (0–1)	0 (0–1)	0.5 (0–2)	
		(*p < .0001)	(*p = .3)	(*p = .5)	
CRP (mg/l)	5 (3–7)	5 (3–6)	5 (3–18)	4 (5–8)	0.6
Before/at the end	3 (1.3–5)	4 (2–5)	5 (2–7)	3 (1–4)	
		(*p = .4)	(*p = .5)	(*p = .1)	
ESSDAI	6 (4–10)	6 (4–10)	6 (4–11)	6 (4–10)	0.6
Before/at the end	4 (2–6)	3 (0–4)	4 (2–6)	4 (3.5–7)	
		(*p < .0001)	(*p = .01)	(*p = .03)	
Steroids dose (mg/day)	10 (7–12.5)	10 (10–15)	10 (5–17.5)	7 (5–10)	0.06
Before/at the end	5 (0 − 10)	5 (0–10)	6 (1–10)	5 (0–6)	
		(*p < .0001)	(*p = .01)	(*p = .03)	

Abbreviations: CRP: C-reactive protein; ESSDAI: EULAR Sjögren Syndrome Disease Activity Index; HCQ: hydroxychloroquine; RTX: rituximab.
* p value between values at the end and before each considered treatment course.

Table 3
Comparison of HCQ, MTX and RTX for joint response (Propensity score).

		OR (IC 95%)	p-Value
Joint non response	MTX vs. HCQ	1.55 [0.18–13.55]	p = .69
	MTX vs RTX	5.08 [0.49–52.17]	p = .17
	HCQ vs. RTX	3.28 [0.28–38.02]	p = .34

Non response is defined as the absence of partial and/or complete joint response.
Abbreviations: HCQ: hydroxychloroquine, MTX: methotrexate, RTX: rituximab.

limits due to missing data. However, our patients' general characteristics do not differ from what has already been described in the literature for pSS patients. Evaluation of treatment efficacy was not randomized and blinded and we considered all treatments courses to analyze the various regimens. Sjögren patients without arthritis were selected from one center (Kremlin-Bicetre Hospital) which could induce some bias of selection and thus we could not evaluate the real prevalence of Sjögren related arthritis. We tried to limit this effect performing a propensity score based analysis, which recently was described for the analysis of series with low patient number. Even well-designed studies are necessary to assess our findings, this first study addressing the efficacy on synovitis in pSS provides data for various treatments efficacies in this specific patient subset, and in particular addresses the steroid sparing effect of different strategies.

In conclusion, pSS articular manifestations may include synovitis which could mimic rheumatoid arthritis, but differ by the absence of structural damage. Even the use of HCQ, MTX and RTX seem to be effective for joint involvement, the best regimen remains to be determined. Only double-blind randomized controlled trial could determine this best regimen for these specific pSS subset.

Conflicts and funding

None.

Conflict of interest

Authors declare not having conflict of interest concerning this work.

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