Original Investigation

Effects of Hydroxychloroquine on Symptomatic Improvement in Primary Sjögren Syndrome
The JOQUER Randomized Clinical Trial

Jacques-Eric Gottenberg, MD, PhD; Philippe Ravaud, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern, MD; Jean Sibilia, MD; Vincent Goeb, MD, PhD; Claire Larroche, MD; Jean-Jacques Dubost, MD; Stéphanie Rist, MD; Alain Saraux, MD; Valérie Devauchelle-Pensec, MD, PhD; Jacques Morel, MD, PhD; Gilles Hayem, MD; Pierre Hatron, MD; Aleth Perdriger, MD; Damien Sene, MD, PhD; Charles Zarnitsky, MD ; Djilali Batouche, MSc; Valérie Furlan, MD; Joelle Benessiano, MD; Elodie Perrodeau, MSc; Raphaele Seror, MD, PhD; Xavier Mariette, MD, PhD

IMPORTANCE Primary Sjögren syndrome is a systemic autoimmune disease characterized by mouth and eye dryness, pain, and fatigue. Hydroxychloroquine is the most frequently prescribed immunosuppressant for the syndrome. However, evidence regarding its efficacy is limited.

OBJECTIVE To evaluate the efficacy of hydroxychloroquine for the main symptoms of primary Sjögren syndrome: dryness, pain, and fatigue.

DESIGN, SETTING, AND PARTICIPANTS From April 2008 to May 2011, 120 patients with primary Sjögren syndrome according to American-European Consensus Group Criteria from 15 university hospitals in France were randomized in a double-blind, parallel-group, placebo-controlled trial. Participants were assessed at baseline, week 12, week 24 (primary outcome), and week 48. The last follow-up date for the last patient was May 15, 2012.

INTERVENTIONS Patients were randomized (1:1) to receive hydroxychloroquine (400 mg/d) or placebo until week 24. All patients were prescribed hydroxychloroquine between weeks 24 and 48.

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients with a 30% or greater reduction between weeks 0 and 24 in scores on 2 of 3 numeric analog scales (from 0 [best] to 10 [worst]) evaluating dryness, pain, and fatigue.

RESULTS At 24 weeks, the proportion of patients meeting the primary end point was 17.9% (10/56) in the hydroxychloroquine group and 17.2% (11/64) in the placebo group (odds ratio, 1.01; 95% CI, 0.37-2.78; $P = .98$). Between weeks 0 and 24, the mean (SD) numeric analog scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in the hydroxychloroquine group. The mean (SD) numeric analog scale score for pain changed from 4.92 (2.94) to 5.08 (2.48) in the placebo group and 5.09 (3.06) to 4.59 (2.90) in the hydroxychloroquine group. The mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group. All but 1 patient in the hydroxychloroquine group had detectable blood levels of the drug. Hydroxychloroquine had no efficacy in patients with anti-SSA autoantibodies, high IgG levels, or systemic involvement. During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group; in the last 24 weeks, there were 3 serious adverse events in the hydroxychloroquine group and 4 in the placebo group.

CONCLUSIONS AND RELEVANCE Among patients with primary Sjögren syndrome, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. Further studies are needed to evaluate longer-term outcomes.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00632866

JAMA. 2014;312(3):249-258. doi:10.1001/jama.2014.7682

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Jacques-Eric Gottenberg, MD, PhD, Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, Centre de Référence National Pour les Maladies Auto-Immunes Systémiques Rares, Université de Strasbourg, 1 Avenue Molière, 67000 Strasbourg, France (jacques-eric.gottenberg@chru-strasbourg.fr); Xavier Mariette, MD, PhD, Service de Rhumatologie, Hôpital Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France (xavier.mariette@bct.aphp.fr).

Primary Sjögren syndrome is a systemic autoimmune disease characterized by dryness, pain, and fatigue. Systemic manifestations occur in approximately one-third of patients.[1] Evidence-based therapy for primary Sjögren syndrome is largely limited to symptomatic treatments of dryness.[2] No conclusions can be drawn regarding the efficacy of biologic treatments currently evaluated, such as rituximab (because of controversial results),[3-5] abatacept (open study published in abstract form), or belimumab (open study).[6] However, the potential safety concerns of these treatments must be taken into account in a disease for which life-threatening complications are infrequent.

Hydroxychloroquine is the immunomodulatory drug most frequently used for primary Sjögren syndrome,[7] usually prescribed for patients with fatigue, arthralgia, and myalgia[8-10] rather than severe systemic manifestations. The latter symptoms are treated with corticosteroids and azathioprine, cyclophosphamide, mycophenolate mofetil, or rituximab. However, despite the wide use of hydroxychloroquine in daily practice, evidence regarding its efficacy is limited. Published data are mostly derived from open or retrospective studies[11-13] and from 1 crossover trial, which included 19 patients.[14] No firm conclusions can be drawn from these results, which were inconsistent in showing some effect of hydroxychloroquine for arthralgia, myalgia, erythrocyte sedimentation rate, and levels of IgG and IgM.

The potential therapeutic interest in hydroxychloroquine for primary Sjögren syndrome has been reinforced by new insights into the pathogenesis of the disease, considered an innate immune-triggered epithelitis resulting from the activation of toll-like receptors, interferon pathways, and B and T lymphocytes.[15] Indeed, one key mechanism of the hydroxychloroquine action was recently revealed as inhibiting the binding of pathogen- and damage-associated molecular patterns to toll-like receptors and subsequent secretion of interferons.[16]

We conducted a multicenter, randomized, placebo-controlled trial to evaluate the efficacy of hydroxychloroquine for the most frequent symptoms of primary Sjögren syndrome: dryness, pain, and fatigue.

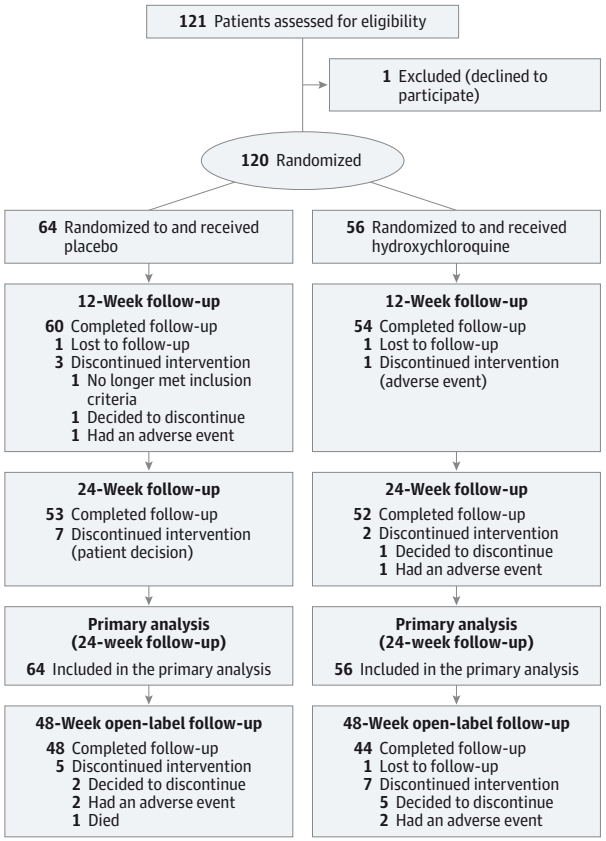
Methods

Design

The protocol was reviewed and approved by the institutional review board of Hôpital Bichat (Paris, France). The study was conducted according to the current regulations of the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Patients were randomly assigned in a 1:1 ratio to receive oral hydroxychloroquine (400 mg/d) or a placebo between weeks 0 and 24 (**Figure 1**). The drug and placebo were indistinguishable in appearance. Randomization was performed by an independent statistician who used a computer-generated list stratified by site. Treatments were assigned after facsimile verification of the correctness of inclusion criteria. Neither the investigators in charge of the study nor the patients were aware of the treatment assignments. Because hydroxychloroquine has a progressive action, could perhaps be more efficacious long term, and is commonly prescribed in daily practice, all patients received hydroxychloroquine during the open phase of the study between weeks 24 and 48.

Figure 1. Flowchart of the Study of Hydroxychloroquine for Symptoms of Primary Sjögren Syndrome



Patients

Fifteen clinical centers in France enrolled patients in the Randomized Evaluation of Hydroxychloroquine in Primary Sjogren's Syndrome (JOQUER) trial (clinicaltrials.gov identifier NCT00632866) between April 2008 and May 2011. The last follow-up date for the last patient was May 15, 2012. To be included, patients had to fulfill the American-European Consensus Group Criteria for primary Sjögren syndrome,[17] be older than 18 years, sign a written informed consent form, have no contraindication to hydroxychloroquine, and be receiving stable doses of nonsteroidal anti-inflammatory drugs, oral corticosteroids, pilocarpine, or topical cyclosporine for at least 4 weeks before enrollment. We excluded patients who previously received hydroxychloroquine, received rituximab or cyclophosphamide during the 6 previous months or any other immunosuppressant during the previous month, and had recent serious systemic manifestations (lymphoma; central nervous system, renal, or pulmonary involvement; myositis; or vasculitis) or severe renal or liver failure. Concomitant treatment with a stable dose of nonsteroidal anti-inflammatory

drugs, oral corticosteroids, pilocarpine, tear substitutes, and topical cyclosporine was allowed.

End Points

The primary end point evaluated at week 24 was the proportion of patients with a 30% or greater reduction from baseline in 2 of 3 of the following: dryness, fatigue, and pain patient-reported scores on a numeric analog scale (0 [best] to 10 [worst]). Improvement in at least 2 of the 3 symptoms was more clinically relevant than improvement in only 1 symptom and corresponded to the same primary end point as in a previous trial,[18] which was helpful to estimate the placebo effect. A post hoc analysis of the same end point was performed at week 48.

Secondary end points were each of the 3 items of the composite primary end point; EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)[19]; EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)[20]; Schirmer test score; unstimulated salivary flow; serum IgG, IgA, and IgM levels; 36-item Medical Outcomes Study Short-Form Health Survey 36 (SF-36) quality-of-life index; Profile of Fatigue and Discomfort (PROFAD); Sicca Symptoms Inventory (SSI)[21]; and Hospital Anxiety and Depression (HAD) scale score. Because we lack a priori–defined minimally clinically important improvement scores for dryness, pain, and fatigue numeric analog scale scores in primary Sjögren syndrome, we estimated the minimally clinically important improvement for each of the 3 scores in a post hoc analysis. Serum levels of immunoglobulins were analyzed at baseline and at week 24 in each center. Blood samples were stored and immediately frozen in the Centre de Ressources Biologiques of Bichat Hospital and the analysis of blood levels of hydroxychloroquine was centralized. Whole blood hydroxychloroquine concentrations were measured by high-performance liquid chromatography with separation on a C18 column after liquid-liquid extraction and fluorescence detection, at excitation 335 nm and emission 405 nm. The limit of quantification was 0.03 mg/L, and the intra-assay and interassay variability was less than 4.5%.[22] Safety evaluation, which included all reports of adverse events, was conducted throughout the study.

Statistical Analysis

The sample size was calculated by using the results of a previous randomized trial, which had the same primary end point.[18] In that study, the placebo effect of an intravenous drug was 26%. Assuming that 20% of patients receiving an oral placebo and 45% of those receiving hydroxychloroquine would show a response, we estimated the target sample size at 60 patients in each group (allowing for a 10% dropout rate; 2-tailed test, $\alpha = .05$; $1 - \beta = .80$).

For the data analysis, statisticians and investigators were unaware of the treatment group allocation. Data were analyzed as intent to treat. Missing data for the primary end point were treated by multiple imputation by chained equation, with $m = 50$ imputations. The covariates used to generate the multiple imputed data sets were age, sex, ESSDAI, ESSPRI, salivary flow rate, Schirmer test score, and disease activity (cardinal signs: pain, fatigue, and dryness), and disease activity (systemic signs) evaluated by the physician on a 0 to 10 numeric analog scale at inclusion.

Categorical variables are described with frequencies and percentages. Quantitative variables are described with the mean (SD) or, if non-normally distributed, median (25th-75th percentile). χ^2 Tests were used to assess differences in categorical variables between the treatment groups at week 24. The analysis was adjusted by center, with mixed logistic regression models to take into account the potential correlation between centers.

To compare differences in changes in values between the 2 treatment groups for quantitative variables, a constrained longitudinal analysis was used. In this model, both the baseline and postbaseline values were modeled as dependent variables, and the true baseline means were constrained to be the same for the 2 treatment groups. Hence, this analysis provides an adjustment for the observed baseline difference in estimating the treatment effects. The differences in differences from week 0 were estimated at each time in each group by the time-by-treatment interaction. Random effects at patient and center levels were added to these models. If the hypotheses for the mixed model were not satisfied, nonparametric analysis was used; distributions in changes between week 0 and the week of interest were compared between the 2 treatment groups by a Wilcoxon test. The secondary analyses were adjusted for multiple comparisons by the Holm-Bonferroni method. Post hoc comparison of the 2 groups was performed at week 48.

In a post hoc analysis, to estimate minimally clinically important improvement scores for pain, fatigue, and dryness numeric analog scale, an anchoring method based on the patient's assessment of evaluation of change in disease activity was used, according to the Outcome Measure in Rheumatology standards.[23] A derivation process was used to calculate the minimally clinically important improvement scores for pain, fatigue, and dryness numeric analog scale. In a 2-stage process, qualitative changes were first measured, and then they were translated to scores. This was done with the whole population of patients included in the trial independently of the treatment allocated. All patients were asked at week 12 whether they felt worse; stable; or somewhat, reasonably, or markedly improved in pain, fatigue, and dryness, using 5-point Likert scales. The minimally clinically important improvement for each of the 3 numeric analog scales (pain, fatigue, and dryness) was estimated by focusing on the population of patients whose week 12 evaluation of change was considered improved. Also, as we aimed at determining minimal important improvement, we excluded patients considered markedly improved. We therefore focused on the population of patients considering their condition reasonably improved and somewhat improved at week 12. The minimally clinically important improvement for each of the 3 numeric analog scale scores (dryness, fatigue, and pain) was defined as a change in the dryness, fatigue, and pain numeric analog scale score that corresponded to the median value of the change in numeric analog scale score in this target population.

All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. Statistical analysis was conducted with R statistical software version 2.14.

Table 1. Baseline Characteristics of Patients With Primary Sjögren Syndrome, by Group (N=120)

	Placebo (n = 64)	Hydroxychloroquine (n = 56)
Age, mean (SD), y	55.6 (13.9)	56.3 (11.9)
Female, No. (%)	60 (93.8)	50 (89.3)
Weight, mean (SD), kg	65.4 (17.2)	65.7 (15.0)
Time to first symptoms, median (25th-75th percentile), y	5 (3-10)	4 (2-10)
Time to diagnosis, median (25th-75th percentile), y	1 (0-5)	1 (1-3)
Focus score[a] ≥1, No. (%)	57 (90.5)	47 (90.4)
Anti-SSA antibodies, No. (%)	34 (54.0)	31 (56.4)
Abnormal Schirmer test result,[b] No. (%)	54 (85.7)	44 (80.0)
Decreased unstimulated salivary flow, No. (%)	31 (60.8)	35 (68.6)
Previous systemic involvement,[c] No. (%)	26 (40.6)	26 (46.4)
Previous treatment with another immunosuppressant, No. (%)	13 (20.3)	10 (17.9)
Current systemic involvement,[d] No. (%)	19 (29.7)	17 (30.4)
ESSDAI[e] median (25th-75th percentile)	2.5 (2.0-6.0)	2.0 (0-5.5)
ESSPRI,[f] mean (SD)	5.85 (2.00)	5.87 (1.96)
NAS scores, mean (SD)		
Dryness	6.38 (2.14)	6.53 (1.97)
Pain	4.92 (2.94)	5.09 (3.06)
Fatigue	6.26 (2.27)	6.00 (2.52)

Abbreviations: ESSPRI, EULAR Sjögren's Syndrome Patient-Related Index (the mean of the 3 NAS scores); NAS, numeric analog scale, from 0 (best) to 10 (worst).

[a] The focus score is the number of mononuclear cell infiltrates containing at least 50 inflammatory cells in a 4-mm 2-glandular section.

[b] Schirmer test ≤5 mm in 5 min.

[c] Previous systemic involvement is defined in the case report form by history of synovitis; myositis; cutaneous, pulmonary, renal, central nervous system, and peripheral nervous system involvement; or lymphoma.

[d] Current systemic involvement is defined in the case report form by presence of synovitis; myositis; or cutaneous, pulmonary, renal, central nervous system, or peripheral nervous system involvement.

[e] Ranging from 0 (best) to 123 (worst).

[f] Ranging from 0 (best) to 10 (worst).

Table 2. For Patients With Active Disease, Domains of the ESSDAI at Enrollment, by Group

	No. (%) of Patients	
ESSDAI Domain[a]	Placebo (n = 64)	Hydroxychloroquine (n = 56)
Articular	27 (42.2)	18 (32.1)
Biological	24 (37.5)	19 (33.9)
Glandular	13 (20.3)	11 (19.6)
Pulmonary	11 (17.2)	10 (17.9)
Hematologic	7 (10.9)	4 (7.1)
Skin	3 (4.7)	0
Peripheral neuropathy	2 (3.1)	3 (5.4)
Constitutional	2 (3.1)	6 (10.7)
Muscular	1 (1.6)	3 (5.4)
Central nervous system	1 (1.6)	1 (1.8)
Lymphadenopathy	1 (1.6)	0
Renal	0	1 (1.8)

[a] Clinical involvement corresponding to each of the 12 domains is defined according to the ESSDAI (European League Against Rheumatism Sjögren's Syndrome Disease Activity Index),[20] ranging from 0 (best) to 123 (worst).

Results

Efficacy

A total of 120 patients were randomized: 56 to hydroxychloroquine and 64 to placebo. The flowchart of the study is in Figure 1. There was no significant difference between the 2 groups in baseline characteristics (**Table 1**). Two patients had a numeric analog scale score of 0 for 2 scales (1 in each group), and 12 patients had a numeric analog scale score of 0 for 1 scale (5 patients receiving placebo; 7, hydroxychloroquine). The proportion of patients who at enrollment had active disease, defined by at least low, moderate, or high disease activity in the domains of the ESSDAI, is in **Table 2**. The median number of active domains in the placebo group was 1 (25th-75th percentile, 1-2) and was also 1 (25th-75th percentile, 0-2) in the hydroxychloroquine group.

At 24 weeks, the proportion of patients meeting the primary end point (≥30% reduction in 2 of the 3 numeric analog scale scores) was 17.9% (10/56) in the hydroxychloroquine group and 17.2% (11/64) in the placebo group (odds ratio, 1.01; 95% CI, 0.37-2.78; P = .98 after multiple imputation) (**Table 3**). Between weeks 0 and 24, the mean (SD) numeric analog scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in hydroxychloroquine group. The mean (SD) numeric analog scale score for pain changed from 4.92 (2.94) to 5.08 (2.48) in the placebo group and 5.09 (3.06) to 4.59 (2.90) in the hydroxychloroquine group. The mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group (**Table 4**).

In post hoc analyses (at week 48), 18.8% (12/64) of the patients receiving placebo between weeks 0 and 24 and then hydroxychloroquine between weeks 24 and 48, and 30.4% (17/56) of those receiving hydroxychloroquine between

Table 3. Patients Reaching the Primary Outcome

	No./Total (%)			
	Placebo	Hydroxychloroquine	OR (95% CI)	*P* Value
Without imputation				
Week 24	9/52 (17.3)	9/51 (17.6)	1.02 (0.36-2.87)	.96
Week 48[a]	8/46 (17.4)	11/40 (27.5)	2.60 (0.91-7.40)	.08
After mean of 50 imputations				
Week 24	11/64 (17.2)	10/56 (17.9)	1.01 (0.37-2.78)	.98
Week 48[a]	12/64 (18.8)	17/56 (30.4)	2.06 (0.66-6.43)	.21

Abbreviation: OR, odds ratio.

[a] Post hoc analysis.

Table 4. Numeric Analog Scale[a] Scores for Dryness, Pain, and Fatigue Between Weeks 0 and 48, by Group

	Placebo		Hydroxychloroquine		Differences in Changes From Baseline (Week 0) Score Adjusted on Baseline Score, Mean (95% CI)	
Domain, by Week	No.	Score, Mean (SD)	No.	Score, Mean (SD)		*P* Value
Dryness						
0	63	6.38 (2.14)	55	6.53 (1.97)		
12	59	6.86 (2.35)	50	6.10 (2.48)	-0.85 (-1.62 to -0.07)	.03
24	53	5.85 (2.57)	51	6.22 (1.87)	0.23 (-0.52 to 0.98)	.55
48[b]	47	5.60 (2.73)	41	5.76 (2.45)	0.04 (-0.83 to 0.92)	.92
Pain						
0	62	4.92 (2.94)	55	5.09 (3.06)		
12	58	5.26 (2.61)	51	4.82 (2.60)	-0.64 (-1.29 to 0.02)	.06
24	52	5.08 (2.48)	51	4.59 (2.90)	-0.71 (-1.46 to 0.04)	.06
48[b]	47	4.81 (2.53)	41	4.29 (2.75)	-0.67 (-1.45 to 0.12)	.10
Fatigue						
0	62	6.26 (2.27)	55	6.00 (2.52)		
12	59	6.32 (1.74)	51	5.90 (2.45)	-0.29 (-0.91 to 0.34)	.37
24	53	5.72 (2.38)	51	5.94 (2.40)	0.25 (-0.56 to 1.05)	.54
48[b]	47	5.47 (2.19)	41	5.61 (2.84)	0.35 (-0.49 to 1.18)	.41

[a] From 0 (best) to 10 (worst).

[b] Post hoc analysis.

weeks 0 and 48, met the primary end point (odds ratio, 2.06; 95% CI, 0.66-6.43; $P = .21$ after multiple imputation) (Table 3). Dryness, pain, and fatigue scores did not differ between weeks 24 and 48 for patients receiving placebo who were prescribed hydroxychloroquine during the open extension phase.

There was no difference between the 2 groups in changes from week 0 in each of the 3 numeric analog scale scores (Table 4) or in the ESSPRI, which is the mean of these 3 scores (**Table 5**). In a post hoc analysis, we calculated the minimally clinically important improvement scores for dryness, pain, and fatigue numeric analog scale scores, which were −1, −1, and −2 points on the 10-point scales, respectively. There was no significant difference between the 2 groups in the proportion of patients with a minimally clinically important improvement score at 6 months in each of the 3 scales or in at least 2 of 3 of the scales, or in the proportion of patients with an improvement of 1, 2, or 3 points in numeric analog scale scores for pain, fatigue, or dryness or in at least 2 of 3 of the scales (**Figure 2**).

In addition, there was no significant difference between the 2 groups in any of the secondary clinical end points, or in systemic disease activity assessed by the ESSDAI or the clinician's numeric analog scale for systemic disease activity (Table 5). Changes in ocular and oral dryness assessed by the Schirmer test and unstimulated salivary flow are reported in Table 5. There was no significant difference between the 2 groups in dryness-related symptoms assessed by the SSI and PROFAD questionnaires, quality of life assessed by the SF-36, or psychological discomfort assessed by the HAD scale (Table 5).

A systemic flare occurred in 4 patients receiving placebo and 5 receiving hydroxychloroquine between weeks 0 and 24 (and in 2 patients and 1 patient, respectively, between weeks 24 and 48).

The 2 treatment groups significantly differed in mean change in erythrocyte sedimentation rate at week 24 (−7.8 [95% CI, −12.0 to −3.7]; $P < .001$) (Table 5). This finding remained the only significant difference after adjustment for multiple comparisons ($P = .007$). The 2 groups differed in mean change in serum IgM levels at week 24 (−0.19 [95% CI, −0.31 to −0.06]; $P = .004$), but not after adjustment for multiple comparisons.

Among the 65 patients with anti-SSA antibodies, 16.1% (5/31) in the hydroxychloroquine group and 23.5% (8/34) in the placebo group met the primary end point at week 24 ($P = .40$), with no difference in change in systemic disease activity

Table 5. ESSPRI, ESSDAI, Evaluation of Disease Activity by Practitioner, Patient-Related Outcome, and Biological Variables, by Group

Parameter, by Week	Placebo No.	Placebo Value, Mean (SD)	Hydroxychloroquine No.	Hydroxychloroquine Value, Mean (SD)	Differences in Changes From Baseline (Week 0) Score Adjusted on Baseline Score, Mean (95% CI)	*P* Value
ESSPRI[a]						
0	62	5.85 (2.00)	55	5.87 (1.96)		
12	58	6.15 (1.72)	50	5.62 (2.14)	-0.57 (-1.10 to -0.05)	.03
24	52	5.58 (1.99)	51	5.81 (1.94)	-0.05 (-0.68 to 0.57)	.87
ESSDAI, median (25th-75th percentile)[b]						
0	64	2.5 (2.0 to 6.0)	55	2.0 (0 to 5.5)		
12	43	2.0 (0 to 4.0)	39	2.0 (0 to 5.5)		
24	52	2.0 (0 to 5.3)	50	2.0 (0 to 3.0)		
12-0	43	0 (-2.0 to 0)	38	0 (-2.0 to 0)		.68
24-0	52	0 (-2.0 to 0)	49	0 (-2.0 to 0)		.63
Cardinal signs (pain, fatigue, dryness) evaluated by practitioner						
0	63	4.67 (2.21)	56	4.5 (1.89)		
24	53	3.98 (2.16)	51	4.08 (1.86)	0.08 (-0.42 to 0.58)	.76
Systemic signs evaluated by practitioner, median (25th-75th percentile)[b]						
0	64	1 (0 to 2.25)	56	1 (0 to 2)		
24	53	1 (0 to 2)	51	1 (0 to 2)		
24-0	53	0 (-1 to 0)	51	0 (0 to 0)		.49
SF-36, physical health component						
0	46	46.9 (19.5)	40	55.5 (21.6)		
24	33	48.1 (19.3)	34	54.5 (20.9)	0.7 (-6.5 to 7.8)	.85
SF-36, mental health component						
0	52	49.2 (20.7)	41	56.5 (19.9)		
24	42	54.4 (22.3)	40	63.1 (17.8)	4.2 (-2.8 to 11.3)	.23
HAD-anxiety						
0	61	9.46 (4.37)	49	9.84 (3.98)		
24	47	7.55 (3.46)	46	9.09 (3.95)	0.32 (-0.71 to 1.36)	.54
HAD-depression						
0	59	6.69 (3.90)	50	6.20 (3.91)		
24	45	5.60 (3.90)	46	6.17 (4.16)	0.57 (-0.43 to 1.58)	.26
Schirmer test, mm						
0	57	6.88 (7.56)	50	8.56 (8.81)		
24	36	7.50 (7.44)	37	10.70 (8.84)	1.05 (-1.54 to 3.65)	.42
0, median (25th-75th percentile)[c]	57	5 (2 to 8)	50	5 (1 to 15)		
24, median (25th-75th percentile)[c]	36	5 (2 to 13)	37	8 (5 to 16)		
Unstimulated salivary flow, mL/min						
0	53	0.16 (0.18)	49	0.17 (0.19)		
24	37	0.18 (0.21)	38	0.22 (0.21)	0.03 (-0.05 to 0.12)	.45
0, median (25th-75th percentile)[c]	53	0.10 (0.03 to 0.22)	49	0.10 (0.06 to 0.23)		
24, median (25th-75th percentile)[c]	37	0.11 (0.02 to 0.22)	38	0.13 (0.06 to 0.30)		
ESR, mm						
0	58	21.0 (14.1)	56	21.5 (23.4)		
24	48	24.7 (16.6)	44	17.5 (21.0)	-7.8 (-12.0 to -3.7)	<.001
0, median (25th-75th percentile)[c]	58	20 (10 to 30)	56	13 (6 to 29)		
24, median (25th-75th percentile)[c]	48	22 (12 to 32)	44	11 (6 to 20)		
C-reactive protein, mg/L						
0	61	4.42 (3.38)	52	4.35 (4.31)		
24	45	6.91 (7.03)	46	4.42 (3.99)	-2.40 (-4.53 to -0.27)	.03
0, median (25th-75th percentile)[c]	61	4 (1 to 6)	52	4 (2 to 6)		
24, median (25th-75th percentile)[c]	45	5 (3 to 6)	46	4 (2 to 6)		

(continued)

Table 5. ESSPRI, ESSDAI, Evaluation of Disease Activity by Practitioner, Patient-Related Outcome, and Biological Variables, by Group (continued)

Parameter, by Week	Placebo No.	Placebo Value, Mean (SD)	Hydroxychloroquine No.	Hydroxychloroquine Value, Mean (SD)	Differences in Changes From Baseline (Week 0) Score Adjusted on Baseline Score, Mean (95% CI)	*P* Value
Serum IgG, g/L						
0	60	14.18 (5.74)	52	14.46 (6.11)		
24	46	14.01 (5.90)	48	13.37 (5.53)	-0.75 (-1.74 to 0.23)	.13
Serum IgA, g/L						
0	60	3.26 (1.74)	51	2.64 (1.16)		
24	45	3.08 (1.38)	48	2.86 (1.89)	0.03 (-0.27 to 0.32)	.85
Serum IgM, g/L						
0	60	1.40 (0.74)	52	1.29 (0.77)		
24	46	1.44 (0.68)	48	1.14 (0.75)	-0.19 (-0.31 to -0.06)	.004

Abbreviations: ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; HAD, Hospital Anxiety and Depression scale; SF-36, 36-item Medical Outcomes Study Short-Form Health Survey.

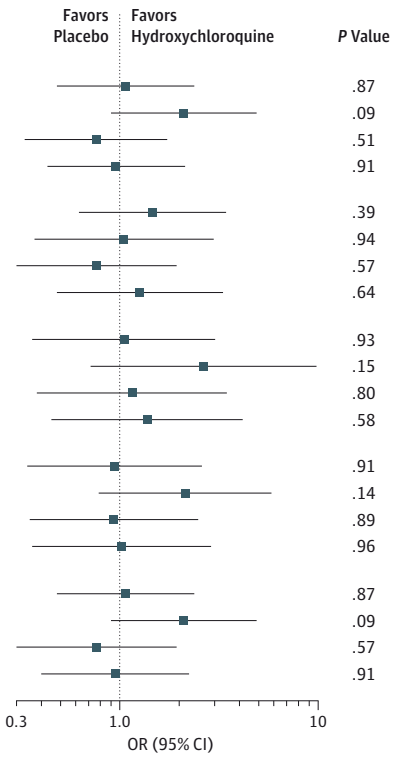
[a] The ESSPRI corresponds to the mean of a patient's numeric analog scale score for dryness, pain, and fatigue.

[b] Data are median (25th-75th percentile), and nonparametric tests were used (Wilcoxon test).

[c] Where the standard deviations exceeded the mean values, medians (25th-75th percentile) are reported as well.

Figure 2. Sensitivity Analyses of the Evolution in Numeric Analog Scale Scores for Pain, Fatigue, and Dryness Among Patients With Primary Sjögren Syndrome

	No. of Events/No. of Patients (%) Placebo	No. of Events/No. of Patients (%) Hydroxychloroquine	OR (95% CI)	*P* Value
Decrease of at least 1 point				
Dryness	22/53 (41.5)	21/50 (42.0)	1.07 (0.48-2.37)	.87
Pain	17/47 (36.2)	25/46 (54.3)	2.10 (0.90-4.89)	.09
Fatigue	21/51 (41.2)	17/49 (34.7)	0.76 (0.33-1.73)	.51
At least 2 of the 3 scales	21/51 (41.2)	20/50 (40.0)	0.95 (0.43-2.13)	.91
Decrease of ≥2 points				
Dryness	14/52 (26.9)	16/49 (32.7)	1.46 (0.62-3.43)	.39
Pain	9/40 (22.5)	10/43 (23.3)	1.04 (0.37-2.97)	.94
Fatigue	14/50 (28.0)	11/48 (22.9)	0.76 (0.30-1.93)	.57
At least 2 of the 3 scales	9/50 (18.0)	10/49 (20.4)	1.26 (0.48-3.31)	.64
Decrease of ≥3 points				
Dryness	8/50 (16.0)	8/49 (16.3)	1.05 (0.36-3.02)	.93
Pain	4/37 (10.8)	9/37 (24.3)	2.65 (0.71-9.81)	.15
Fatigue	7/48 (14.6)	7/44 (15.9)	1.15 (0.38-3.46)	.80
At least 2 of the 3 scales	6/48 (12.5)	7/45 (15.6)	1.37 (0.45-4.16)	.58
Decrease of ≥30%				
Dryness	10/53 (18.9)	9/50 (18.0)	0.94 (0.34-2.59)	.91
Pain	8/47 (17.0)	14/46 (30.4)	2.13 (0.78-5.81)	.14
Fatigue	11/51 (21.6)	10/49 (20.4)	0.93 (0.35-2.48)	.89
At least 2 of the 3 scales	9/51 (17.6)	9/50 (18.0)	1.02 (0.36-2.88)	.96
Decrease reaching MCII				
Dryness (1point)	22/53 (41.5)	21/50 (42.0)	1.07 (0.48-2.37)	.87
Pain (1 point)	17/47 (36.2)	25/46 (54.3)	2.10 (0.90-4.89)	.09
Fatigue (2 points)	14/50 (28.0)	11/48 (22.9)	0.76 (0.30-1.93)	.57
At least 2 of the 3 scales	16/50 (32.0)	15/49 (30.6)	0.95 (0.40-2.23)	.91



The numeric analog scale ranges from 0 (best) to 10 (worst). MCII indicates minimally clinically important improvement. Actual values of odds ratio are plotted on a log scale.

assessed by the ESSDAI (median change between week 24 and week 0 of 0 [25th-75th percentile, −2 to 0] and 0 [25th-75th percentile, −2 to 0.5]; *P* = .82). Among the 36 patients with systemic involvement (defined in the case report form by presence of synovitis, myositis, or cutaneous, pulmonary, renal, central nervous system, or peripheral nervous system involvement), 29.4% (5/17) in the hydroxychloroquine group and 21.0% (4/19) in the placebo group met the primary end point at week 24 (*P* = .66), with no difference in change in ESSDAI (median change between weeks 24 and 0 of −2 [25th-75th percentile,

Table 6. Serious Adverse Events in Patients With Primary Sjögren Syndrome by Treatment

Serious Adverse Event	No. (%)	
	Placebo (n = 64)	Hydroxychloroquine (n = 56)
Between weeks 0 and 24	3 (4.7)	2 (3.6)
Type of serious adverse event		
Urinary lithiasis	0	1
Surgery for meningioma	1	0
Lipothymia	1	0
Breast cancer	0	1
EBV and CMV pneumonia	1	0
Between weeks 24 and 48	4 (6.2)	3 (4.7)
Type of serious adverse event		
Pneumococcal meningitis and death	1	0
Optical neuropathy	1	0
Diverticulosis-relayed gastrointestinal bleeding	0	1
Multiple myeloma	0	1
Acute coronary syndrome	0	1
Acute exanthematous pustulosis	1	0
Severe diarrhea	1	0
Total events	7	5

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus.

−2.5 to −0.5] and 0 [25th-75th percentile, −4 to 0]; $P = .67$). Likewise, hydroxychloroquine was not efficacious in the 45 patients with articular involvement, including 40 patients with arthralgias and 5 with synovitis. Among the 56 patients with high IgG levels (baseline serum IgG level ≥12.6 g/L [median value for the 120 patients]), 19.2% (5/26) and 23.3% (7/30) met the primary end point at week 24 in the hydroxychloroquine and placebo groups, respectively ($P = .81$), with no difference in change in ESSDAI (median change between week 24 and week 0 of 0 [25th-75th percentile, −2.0 to 0] and −0.5 [25th-75th percentile, −2.5 to 0.5]; $P = .78$).

Data from the centralized analysis of blood hydroxychloroquine levels were available at week 24 for 42 of the 56 patients in the hydroxychloroquine group; 41 showed blood levels of hydroxychloroquine. Among the 42 of 56 patients in the hydroxychloroquine group with assessed blood levels of hydroxychloroquine at week 24, blood levels of hydroxychloroquine were not associated with the primary outcome at week 24 (22.7% of responders in patients with blood levels >0.7 mg/L vs 25.0% of responders in patients with blood levels ≤0.7 mg/L; odds ratio, 0.88 [95% CI, 0.21-3.73]; $P = .86$) or with change in ESSDAI (median change between weeks 24 and 0 of −1 [−2 to 0] and 0 [−2 to 0], respectively; $P = .68$).

Tolerance

During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group. In the last 24 weeks, there were 3 in the hydroxychloroquine group and 4 in the placebo group (**Table 6**). One patient who received placebo died from pneumococcal meningitis.

Discussion

In the present study, hydroxychloroquine did not demonstrate efficacy for the main disabling symptoms—dryness, pain, and fatigue—of primary Sjögren syndrome compared with placebo. The JOQUER trial extends the negative results of the only previous controlled crossover trial, which included 19 patients[14] and confirms that previous open trials might have overestimated the therapeutic efficacy of hydroxychloroquine in primary Sjögren syndrome.

The findings in this study should be interpreted with consideration of several methodological limitations. Regarding the design of the trial, we performed a classic randomized clinical trial rather than a discontinuation trial, which previously demonstrated the efficacy of hydroxychloroquine in reducing clinical flares of systemic lupus erythematosus.[24] A consensus definition of flares in primary Sjögren syndrome is lacking, and flares are more infrequent in primary Sjögren syndrome than systemic lupus erythematosus (12 flares in 120 patients followed for 12 months in the JOQUER trial compared with 25 flares in 47 patients followed for 6 months in the systemic lupus erythematosus trial[24]). Our inclusion criteria were not restrictive (fulfillment of American-European Consensus Group Criteria diagnostic criteria, absence of previous treatment with hydroxychloroquine) because hydroxychloroquine is largely prescribed and recommended in clinical practice for patients with low or mild disease activity.[7-10] In addition, for ethical reasons, patients with serious systemic manifestations would not be included in a placebo-controlled trial. These features might explain the lower proportion of patients with anti-SSA antibodies and high immunoglobulin levels, 2 characteristics associated with increased systemic disease activity, and of patients with high systemic disease activity than in some cohorts of patients followed in tertiary centers.

Because consensus is lacking on the choice of primary outcome in clinical trials of primary Sjögren syndrome, we focused on the main symptoms of the disease that concern most patients with the syndrome: dryness, pain, and fatigue. This pragmatic approach was justified by hydroxychloroquine being prescribed in daily practice for these symptoms. The reduction of 30% in at least 2 numeric analog scale scores for dryness, pain, and fatigue is debatable but allowed estimating the sample size, taking into account the placebo response of the infliximab trial, which had the same response criteria.[18] The present trial allowed estimating the minimally clinically important improvement for the numeric analog scale scores for dryness, pain, and fatigue. Sensitivity analyses revealed no significant difference between hydroxychloroquine and placebo in 6-month proportion of patients with a minimally clinically important improvement for each of the 3 scores or at least 2 of 3 scores. The recently validated systemic disease activity score, the ESSDAI, was not available in its definitive form when the trial was initiated and could not be used as the primary end point. In addition, using change in ESSDAI as a primary outcome requires including only patients with substantial systemic disease activity. Thus, any choice of study end points in

primary Sjögren syndrome is questionable. Limitations of the study also include the absence of participant assessment of adequacy of blinding.

The absence of superiority of 6 months of hydroxychloroquine over placebo was consistent whatever the clinical variable evaluated. We observed no difference with the 2 treatments in objective features of dryness, disease-related discomfort, or quality of life assessed by validated questionnaires. Regarding dryness, few patients had short disease duration, which is associated with better efficacy of rituximab for dryness.[25,26] Although no patient had high systemic disease activity, one-third of our patients had at least 1 systemic sign at enrollment. We observed no significant change in the ESSDAI or the clinician's numeric analog scale score for systemic disease activity. Hydroxychloroquine, which is often prescribed for arthralgia, was not superior to placebo in patients with articular involvement. However, the number of patients with synovitis was too limited to draw any conclusions on the use of hydroxychloroquine in this setting. Considering the primary end point or sensitivity analysis (Figure 2), hydroxychloroquine had some efficacy, but not significantly, for pain compared with placebo. Hydroxychloroquine has been described as potentially effective in patients with purpura, mainly if associated with hypergammaglobulinemia. Only 3 of our patients, all in the placebo group, had purpura, which precludes any conclusion concerning the skin involvement. Levels of IgM decreased, which resulted in a significant decrease in erythrocyte sedimentation rate in the hydroxychloroquine group. All the prespecified end points were evaluated at 6 months, a duration considered sufficient in systemic lupus erythematosus trials, and then, in post hoc analyses, at 12 months, a duration used in some rheumatoid arthritis trials.[27]

The absence of hydroxychloroquine efficacy was not related to poor adherence to treatment, as was reported for patients with systemic lupus erythematosus.[28] All but 1 patient in the hydroxychloroquine group had detectable blood hydroxychloroquine levels at week 24. In addition, the biological effect of hydroxychloroquine was demonstrated by a decrease in levels of serum IgG and IgM, and in erythrocyte sedimentation rate, as was reported in previous trials of hydroxychloroquine in primary Sjögren syndrome.[11-14] Such a decrease might result from the different mechanisms of action of hydroxychloroquine: inhibition of human leukocyte antigen class II expression, autophagy, type I interferon, and other proinflammatory cytokines, as well as induction of regulatory T cells.[29] Even when restricting the analysis to patients with high blood levels of hydroxychloroquine or with strong features of immune activation such as anti-SSA antibodies or high IgG level, no efficacy of hydroxychloroquine could be demonstrated.

Conclusions

Among patients with primary Sjögren syndrome, the use of hydroxychloroquine did not improve symptoms during 24 weeks of treatment compared with placebo. Further studies are needed to evaluate longer-term outcomes.

ARTICLE INFORMATION

Author Affiliations: Department of Rheumatology, Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, Centre de Référence National Pour les Maladies Auto-Immunes Systémiques Rares, Université de Strasbourg, Strasbourg, France (Gottenberg, Sibilia); Department of Epidemiology and Public Health, Hotel Dieu, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France (Ravaud, Perrodeau); Department of Internal Medicine, Cochin Hospital, AP-HP, Paris, France (Puéchal, Le Guern); Department of Rheumatology, Amiens University Hospital, Amiens, France (Goeb); Department of Internal Medicine, Avicenne Hospital, AP-HP, Bobigny, France (Larroche); Department of Rheumatology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France (Dubost); Department of Rheumatology, Orléans Hospital, Orléans, France (Rist); Department of Rheumatology, Brest University Hospital, Brest, France (Saraux, Devauchelle-Pensec); Department of Rheumatology, Montpellier University Hospital, Montpellier, France (Morel); Department of Rheumatology, Hôpital Bichat, AP-HP, Paris, France (Hayem); Department of Internal Medicine, Lille University Hospital, Lille, France (Hatron); Department of Rheumatology, Rennes University Hospital, Rennes, France (Perdriger); Department of Internal Medicine, Lariboisère Hospital, AP-HP, Paris, France (Sene); Department of Rheumatology, Le Havre Hospital, Le Havre, France (Zarnitsky); Department of Rheumatology, Hôpitaux Universitaires Paris-Sud, AP-HP, INSERM U 1012, Université Paris Sud, Le Kremlin Bicêtre, France (Batouche, Seror, Mariette); Department of Pharmacy, Hôpitaux Universitaires Paris-Sud, AP-HP, Le Kremlin Bicêtre, France (Furlan); Department of Centre de Ressources Biologiques, Bichat Hospital, AP-HP, Paris, France (Benessiano).

Author Contributions: Dr Ravaud and Ms Perrodeau had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gottenberg, Ravaud, Le Guern, Sibilia, Dubost, Morel, Sene, Zarnitsky, Furlan, Benessiano, Seror, Mariette.
Acquisition, analysis, or interpretation of data: Gottenberg, Ravaud, Puéchal, Sibilia, Goeb, Larroche, Dubost, Rist, Saraux, Devauchelle-Pensec, Morel, Hayem, Hatron, Pedriger, Sene, Zarnitsky, Batouche, Perrodeau, Seror, Mariette.
Drafting of the manuscript: Gottenberg, Ravaud, Sibilia, Goeb, Sene, Zarnitsky, Perrodeau, Mariette.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ravaud, Devauchelle-Pensec, Zarnitsky, Perrodeau, Seror.
Obtained funding: Gottenberg, Ravaud, Dubost, Rist, Sene, Zarnitsky, Mariette.
Administrative, technical, or material support: Gottenberg, Ravaud, Puéchal, Goeb, Saraux, Sene, Zarnitsky, Batouche, Furlan, Benessiano, Mariette.
Study supervision: Gottenberg, Sibilia, Goeb, Saraux, Hatron, Pedriger, Sene, Zarnitsky, Batouche, Mariette.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gottenberg reports receiving grants from Abbvie, Pfizer, and Roche and personal fees from Bristol-Myers Squibb, Merck Sharpe and Dohme, and Pfizer for activities outside the submitted work. Dr Morel reports receiving fees for consulting from Roche for activities outside the submitted work. Dr Seror reports receiving consulting fees from Roche, Bristol-Myers Squibb, and Pfizer, and grants from EULAR and GlaxoSmithKline for research on Sjögren syndrome. Dr Mariette reports receiving fees from Roche, Pfizer, UCB, Bristol-Myers Squibb, and GlaxoSmithKline for activities outside the submitted work and grants from Roche, Pfizer, Bristol-Myers Squibb, GlaxoSmithKline, and Biogen. No other authors reported disclosures.

Funding/Support: The study was sponsored by Assistance Publique-Hôpitaux de Paris, with a grant from the French Ministry of Research (Programme Hospitalier de Recherche Clinique National 2007 P070125). sanofi-aventis provided hydroxychloroquine and placebo.

Role of the Sponsor: None of the funding sources had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Myriem Carrier, MSc, Direction de la Recherche Clinique, Assistance Publique-Hôpitaux de Paris for helping us set up the study; Karine Inamo, MSc, Stanie Gaete, MSc, Cecile Etienne, MSc, Laina N'Diaye, MSc, and Hélène Agostini, MD, Unité de Recherche Clinique Paris-Sud, Le Kremlin Bicêtre, for

monitoring the study; Mickael Randrianandrasana, MSc, and Isabelle Pane, MSc, Department of Epidemiology and Public Health, Hotel Dieu Hospital, Paris, for data management; and Virginie Huart, MSc, Centre de Ressources Biologiques of Bichat Hospital, for the storage of blood samples. No one received compensation for his or her contribution to the study.

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