Annals of Internal Medicine | ORIGINAL RESEARCH

Treatment of Primary Sjögren Syndrome With Rituximab

A Randomized Trial

Valérie Devauchelle-Pensec, MD, PhD; Xavier Mariette, MD, PhD; Sandrine Jousse-Joulin, MD; Jean-Marie Berthelot, MD; Aleth Perdriger, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern, MD, PhD; Jean Sibilia, MD, PhD; Jacques-Eric Gottenberg, MD, PhD; Laurent Chiche, MD, PhD; Eric Hachulla, MD, PhD; Pierre Yves Hatron, MD; Vincent Goeb, MD, PhD; Gilles Hayem, MD; Jacques Morel, MD, PhD; Charles Zarnitsky, MD; Jean Jacques Dubost, MD; Jacques Olivier Pers, MD, PhD; Emmanuel Nowak, PhD; and Alain Saraux, MD, PhD

Background: Primary Sjögren syndrome (pSS) is an autoimmune disorder characterized by ocular and oral dryness or systemic manifestations.

Objective: To evaluate efficacy and harms of rituximab in adults with recent-onset or systemic pSS.

Design: Randomized, placebo-controlled, parallel-group trial conducted between March 2008 and January 2011. Study personnel (except pharmacists), investigators, and patients were blinded to treatment group. (ClinicalTrials.gov: NCT00740948)

Setting: 14 university hospitals in France.

Patients: 120 patients with scores of 50 mm or greater on at least 2 of 4 visual analogue scales (VASs) (global disease, pain, fatigue, and dryness) and recent-onset (<10 years) biologically active or systemic pSS.

Intervention: Randomization (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo.

Measurements: Primary end point was improvement of at least 30 mm in 2 of 4 VASs by week 24.

Results: No significant difference between groups in the primary end point was found (difference, 1.0% [95% CI, −16.7% to 18.7%]). The proportion of patients with at least 30-mm decreases in at least two of the four VAS scores was higher in the rituximab group at week 6 (22.4% vs. 9.1%; $P = 0.036$). An improvement of at least 30 mm in VAS fatigue score was more common with rituximab at weeks 6 ($P < 0.001$) and 16 ($P = 0.012$), and improvement in fatigue from baseline to week 24 was greater with rituximab. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab.

Limitation: Low disease activity at baseline and a primary outcome that may have been insensitive to detect clinically important changes.

Conclusion: Rituximab did not alleviate symptoms or disease activity in patients with pSS at week 24, although it alleviated some symptoms at earlier time points.

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For author affiliations, see end of text.

Primary Sjögren syndrome (pSS) is a chronic autoimmune disorder characterized by dryness of the eyes and mouth and systemic involvement in up to 50% of cases (1). Histopathology shows lymphocytic infiltration and destruction of the lachrymal and salivary glands (2). To date, no systemic treatment has been proved to significantly affect the course of pSS (3), but clinicians may prescribe hydroxychloroquine to patients having fatigue or arthralgia and corticosteroids, methotrexate, or immunosuppressants to patients with systemic involvement. Because mounting evidence points to a central pathophysiologic role for B cells (4–7), B-cell depletion is being evaluated as a treatment of pSS (8–11).

The most widely studied target for achieving B-cell depletion is the CD20 antigen, a transmembrane protein found on pre-B and mature B cells. It is neither shed from the cell surface nor internalized on antibody binding (12–14). In open-label studies, the anti-CD20 antibody rituximab had a good safety profile, induced rapid B-cell depletion in blood and salivary glands, and seemed beneficial in early active pSS and in pSS with active extraglandular involvement (8, 9, 15). Two small, double-blind, randomized trials have been published (10, 11). The first included 18 patients and suggested an effect on the visual analogue scale (VAS) fatigue score after 6 months, although the primary end point, a 20% or greater decrease in the VAS fatigue score, was not achieved (10). The second trial included 30 patients with recent active pSS and showed improvements in the VAS dryness score and stimulated total salivary flow rate after 6 months (11).

The purpose of the randomized, placebo-controlled TEARS (Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome) trial reported here was to evaluate the efficacy and adverse effects of rituximab in pSS.

METHODS

Design Overview

This randomized, placebo-controlled, parallel-group trial evaluated global disease, pain, fatigue, and dryness. French rheumatologists and internists recruited the pa-

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Context

Few trials have examined treatments for primary Sjögren syndrome (pSS).

Contribution

This multicenter, double-blind, placebo-controlled, randomized trial found that rituximab (given in 2 infusions over 2 weeks) alleviated some symptoms at week 6 but did not alleviate symptoms or improve global activity score at month 6 in adults with recent-onset or systemic pSS. More infusion reactions occurred with rituximab than placebo.

Caution

Outcome measurements may have been insensitive for detecting improvement.

Implication

Rituximab infusions did not produce sustained or substantial alleviation of symptoms or improvement in disease activity in adults with recent-onset or systemic pSS.

—The Editors

tients between 6 March 2008 and 5 January 2011. Patients were randomly assigned in a 1:1 ratio to blinded treatment with intravenous infusions of rituximab (1 g) or placebo at weeks 0 and 2. All study personnel, investigators, and patients remained blinded to the treatment group throughout the study. This study was approved by the appropriate ethics committee (CPP Ouest VI), and all patients gave written informed consent before study enrollment. The protocol was registered on ClinicalTrials.gov (NCT00740948).

Setting and Participants

Patients were recruited at 14 university hospitals in France if they fulfilled the American–European Consensus Group criteria for pSS (16) and had active disease, defined as scores of at least 50 mm on at least 2 of 4 VASs (scores range from 0 [none] to 100 mm [worst]) for global disease, pain, fatigue, and dryness. Additional requirements were onset of pSS symptoms (first visit for any sign) in the past 10 years and biologically active pSS (defined as autoantibodies [anti-Ro/SSA antibodies or rheumatoid factor], cryoglobulinemia, hypergammaglobulinemia, β_2-microglobulin elevation, or hypocomplementemia) or systemic pSS with at least 1 extraglandular manifestation or current parotid gland enlargement. The other inclusion criteria were informed consent, being aged 18 to 80 years, stable nonsteroidal anti-inflammatory drug regimen, no use of immunosuppressive agents for at least 4 weeks before inclusion, and use of an effective contraceptive method for patients able to conceive. Exclusion criteria were secondary Sjögren syndrome; cytotoxic drug therapy in the past 4 months; severe renal or hematologic failure; history of cancer, hepatitis B or C, HIV infection, tuberculosis, severe diabetes, or any other chronic disease; evidence of infection; history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies; and an inability to understand the study protocol.

Randomization and Interventions

Randomization was stratified by site. A computer-generated random allocation sequence was prepared by our statistics department in Brest, France. The infusions were prepared after a telephone call to the statistics department by pharmacists who were not involved in any other study procedure and were instructed not to disclose the treatment group to the investigators. All patients received the same volume, but the infusion contained the solvent only (normal saline or 5% glucose) in the placebo group and the solvent plus rituximab in the rituximab group. Before each rituximab or placebo infusion, the patients received 100 mg of methylprednisolone intravenously and 500 mg of acetaminophen orally.

Outcomes and Follow-up

Efficacy was evaluated at weeks 6, 16, and 24. The primary outcome, chosen a priori on the basis of expert opinion, was a 30-mm or greater improvement at week 24 versus baseline on at least 2 of the 4 VAS scores.

Secondary outcomes included variations from baseline in the individual VAS scores at weeks 6 and 16; disease activity, systemic manifestations, and treatment activity assessed by the investigator as present or absent and by using both a physician VAS for disease activity and the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI), a clinical index that is designed to measure disease activity in patients with pSS (12 domains with a total score ranging from 2 to 47) (17, 18); basal salivary flow rate; Schirmer test and van Bijsterveld scores and Chisholm grade (19, 20); C-reactive protein level and erythrocyte sedimentation rate; rheumatoid factor; antinuclear antibodies; serum IgG, IgA, and IgM levels; serum complement; cryoglobulinemia; and serum level of B-cell–activating factor (BAFF) (21).

Clinicians collected open-ended adverse events and assessed severity and potential causality at each visit from baseline to week 24. At study completion, the chief investigator categorized the adverse events according to the Medical Dictionary for Regulatory Activities, which is required by European regulations. We used Lower-Level Terms in the System Organ Class system.

Statistical Analysis

Our power calculation was based on our primary end point assessed at week 24. To detect a difference of 30 percentage points between groups in the proportion of patients achieving the primary end point, with a 2-sided α of 0.05 and 80% power, we needed 49 patients per group. We planned to enroll 120 patients to allow for withdrawals and missing data.

All randomly assigned patients who did not withdraw before the first study-drug infusion were included in the

efficacy analyses. They were analyzed in the group to which they had been randomly assigned, even when a protocol deviation was reported (intention-to-treat principle). We used a fully conditional specification method to do multiple imputation and to handle missing data, which were assumed to be missing at random. We used the MICE function in R, version 2.14 (R Foundation for Statistical Computing, Vienna, Austria), to generate 20 imputed data sets. The initial data set to impute contained all outcomes of interest, baseline characteristics, and center and random assignments. To build the imputation model, we used the quickpred function in R to include all predictors with an absolute correlation of at least 0.2 with the target or the response indicator. Study center and treatment group were forced to be included in the imputation model. Continuous variables that were clearly nonnormal were transformed before imputation then back-transformed to create the final imputed data set.

We analyzed the primary outcome at week 24 using a generalized linear model with binomial distribution, identity link, and exchangeable correlation structure to account for study center. Although identity is not the usual link for a binary response, it can be used in the present situation (22, 23) to estimate a risk difference with the CI, as recommended by the CONSORT (Consolidated Standards of Reporting Trials) statement. Secondary outcomes were analyzed by using the same statistical method, except a normal distribution was used for continuous data. All efficacy analyses were first done for each week by using the imputed data, except for the serum BAFF level, which was not collected in all study centers and was analyzed by using the observed data. Reductions in BAFF levels were compared between the rituximab and placebo groups by using the Wilcoxon test.

For the 4 VASs used to define the primary end point, longitudinal analyses were then done on the observed data by using a mixed model. In these analyses, we used treatment group, visit, and the visit–treatment group interaction term as independent variables; study center as a random-effects factor; a compound symmetry covariance structure to account for repeated measures among visits; and age, sex, baseline antibody values, and recent-onset or systemic pSS information as covariates.

We used SAS, version 9.3 (SAS Institute, Cary, North Carolina), for all analyses except for multiple imputation, for which we used R, version 2.14. *P* values less than 0.05 were considered statistically significant. We used the MICE function in R to generate imputed data sets, PROC MIANALYZE in SAS to obtain pooled estimates, and PROC GENMOD and PROC MIXED in SAS to build generalized linear models and mixed models and to make statistical inferences based on *t* tests or *F* tests. Graphical representations of longitudinal data were obtained from estimates given by the LSMEANS statement of the MIXED procedure in SAS. This allowed a representation of the course of VAS values when identical baseline characteristics that were taken to be equal to the mean values were assumed.

We did sensitivity analyses to check the robustness of the results according to the method used to handle missing data (**Appendix Table 1**, available at www.annals.org). First, analyses were done only on available data, assuming that data were missing completely at random. Second, the missing data for pain, fatigue, dryness, and global VAS scores (≥30-mm decrease) at weeks 6, 16, and 24 were imputed as a failure to investigate the effects on statistical results if the data would have been more likely to be missing in patients without improvements of at least 30 mm. Models used for sensitivity analyses were the same as for the primary analyses (for example, the generalized linear model).

Role of the Funding Source

The Programme Hospitalier de Recherche Clinique 2010 (the French public research funding agency) funded this study. Rituximab was donated free of charge by Roche (Boulogne Billancourt, France). Neither the funding source nor Roche had any role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, revision, or approval of the manuscript.

RESULTS

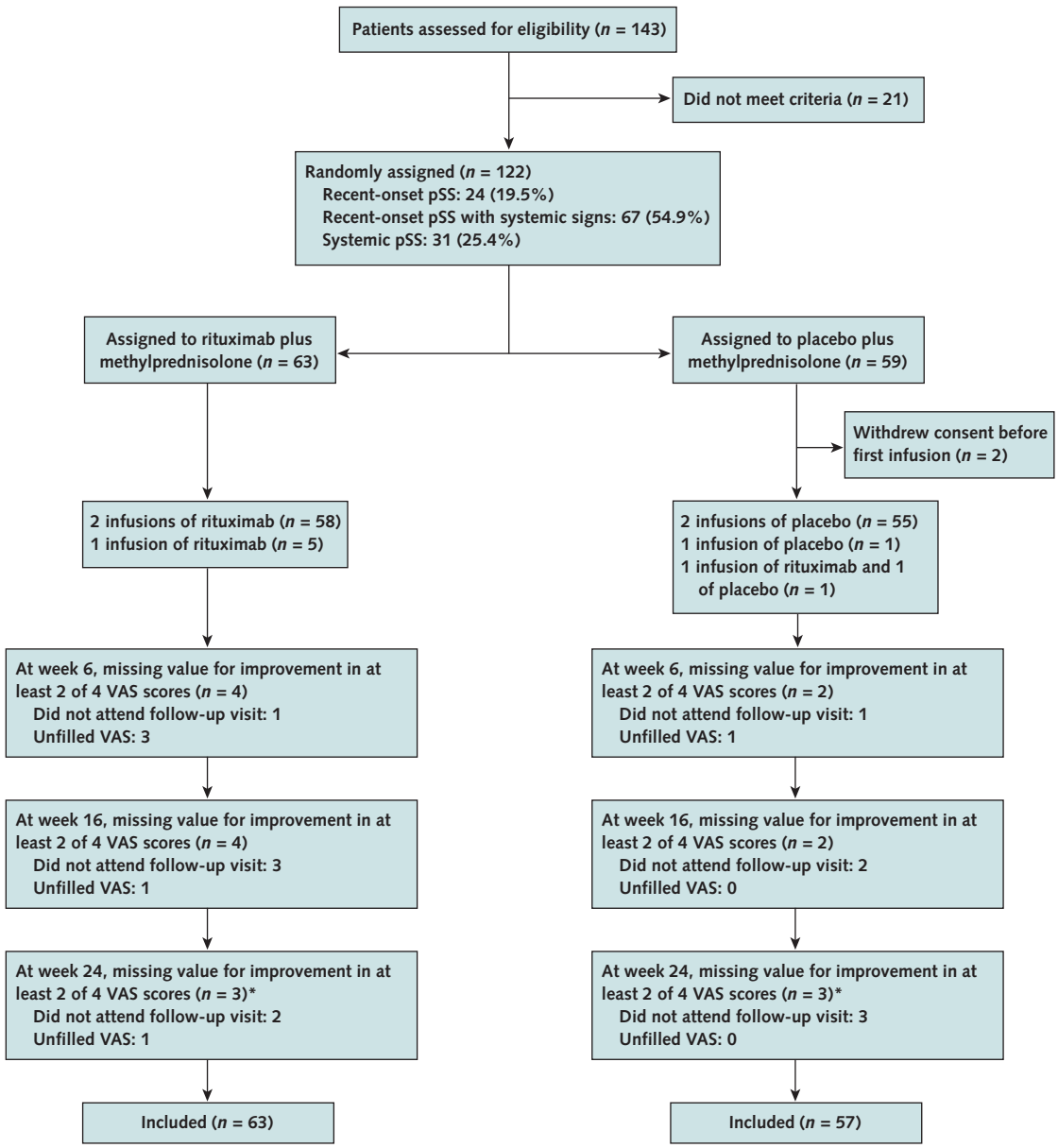
Patient Characteristics

We randomly assigned 122 patients with pSS, including 24 with recent-onset pSS, 31 with systemic pSS, and 67 with both. Among them, 120 received at least 1 infusion and were included in the analysis (**Figure 1**). Five patients in the rituximab group and 1 in the placebo group did not receive the second infusion because of adverse events. Baseline characteristics were similar between groups (**Table 1**). Most patients were women; 97 (80.8%) had anti-Ro/SSA or anti-La/SSB antibodies, and 105 (87.5%) had abnormal salivary gland biopsy results (focus score ≥1). The mean ESSDAI score was 10.1 (SD, 6.8). Mean global disease VAS scores in the placebo and rituximab groups were 69.4 (SD, 17.0) and 68.9 (SD, 15.6), respectively. The primary co-interventions that patients received were steroid therapy (34 patients), methotrexate (17 patients), and local therapy, but their variations were considered negligible by the investigators during follow-up.

Efficacy

At weeks 6, 16, and 24, the percentages of patients with decreases of at least 30 mm in at least 2 of the 4 VAS scores were 9.1%, 17.0%, and 22.0%, respectively, in the placebo group and 22.4%, 26.3%, and 23.0%, respectively, in the rituximab group. The percentage was larger in the rituximab group only at week 6 (difference, 13.3 percentage points [95% CI, 0.8 to 25.8 percentage points]; $P = 0.036$) (**Table 2**). For the primary outcome (week 24), the difference (1.0 percentage point [CI, −16.7 to

Figure 1. **Study flow diagram.**



pSS = primary Sjögren syndrome; VAS = visual analogue scale.
* Primary outcome is improvement in ≥2 of 4 VAS scores at week 24.

18.7 percentage points]) was not significant. The sensitivity analysis confirmed the robustness of our results (**Supplement**, available at www.annals.org).

Table 2 reports the secondary efficacy outcomes (proportion of patients having an improvement and magnitude of the improvement). A 30-mm decrease in the VAS fatigue score was more common with rituximab than placebo at week 6 (absolute difference, 26.6 percentage points [CI, 15.7 to 37.5 percentage points]; $P < 0.001$) and week 16 (absolute difference, 18.3 percentage points [CI, 4.1 to 32.6 percentage points]; $P = 0.012$). The difference in the percentage of patients with a VAS dryness score that decreased by at least 30 mm at any of the time points was not clinically significant between groups (absolute differences of 8.0 percentage points [CI, −3.7 to 19.7 percentage points], 7.5 percentage points [CI, −5.4 to 20.4 percentage points], and 12.4 percentage points [CI, −3.0 to 27.8 percentage points] at weeks 6, 16, and 24, respectively).

Figure 2 shows the course of VAS scores from baseline to week 24 in the rituximab and placebo groups after adjustment for baseline characteristics, as well as results of longitudinal data analyses. The mean decrease in the VAS

fatigue score was larger with rituximab than placebo at weeks 6, 16, and 24. Pain was not alleviated by rituximab at any of the evaluation time points. The **Supplement** shows data plots for each patient over time by baseline value (≤50 or >50 mm).

At week 6, more patients in the rituximab group than the placebo group had improvements in physician-assessed disease activity (absolute difference, 19.1 percentage points [CI, 4.4 to 33.7 percentage points]), treatment efficacy (absolute difference, 21.0 percentage points [CI, 9.3 to 32.7 percentage points]), and global VAS score (mean difference, 8.4 mm [CI, 4.2 to 12.5 mm]); this was not the case at weeks 16 or 24 (**Table 2**). The decrease in ESSDAI score was not larger with rituximab than placebo at week 6 (mean difference, −0.3 [CI, −1.2 to 0.7]), week 16 (mean difference, −0.3 [CI, −1.7 to 1.0]), or week 24 (mean difference, −0.5 [CI, −2.3 to 1.3]), including for the biological domain (**Supplement**). The proportions of patients with systemic pSS who had resolution of parotid gland enlargement or joint involvement were not higher with rituximab than placebo (40 of 54 patients [74.1%] in the placebo group and 47 of 61 patients [77%] in the rituximab group had an ESSDAI glandular item scored 0 at week 24 [**Appendix Table 2**, available at www.annals.org]).

At week 24, serum IgG, IgA, IgM, and β_2-microglobulin levels were more improved with rituximab (IgG difference, 1.2 g/L [CI, 0.4 to 2.0 g/L]; $P = 0.003$; IgA difference, 0.5 g/L [CI, 0.0 to 1.1 g/L]; $P = 0.047$; IgM difference, 0.3 g/L [CI, 0.2 to 0.4 g/L]; $P < 0.001$; β_2-microglobulin difference, 1.6 g/L × 10^{-4} [CI, 0.5 to 2.8 g/L × 10^{-4}]; $P = 0.004$).The serum BAFF levels at baseline and week 24 were 4.63 ng/mL (SD, 12.42 ng/mL) and 2.43 ng/mL (SD, 7.31 ng/mL), respectively, in the rituximab group and 6.05 ng/mL (SD, 10.08 ng/mL) and 5.1 ng/mL (SD, 9.06 ng/mL), respectively, in the placebo group. The decrease was not larger with rituximab than placebo (−2.20 ng/mL [SD, 6.07 ng/mL] vs. −0.89 ng/mL [SD, 6.82 ng/mL]; $P = 0.38$).

Adverse Events

Table 3 reports adverse events, severe adverse events, and discontinuation due to adverse events. Infusion reactions were significantly more common in the rituximab group (**Appendix Table 3**, available at www.annals.org). The only other significant between-group difference occurred for the proportion of patients who had at least 1 respiratory disorder ($P = 0.014$) within 24 hours after an infusion. Shortness of breath ($n = 1$), dry cough ($n = 1$), sneezing ($n = 1$), or throat irritation ($n = 5$) were recorded in 7 patients receiving rituximab. Only 1 respiratory disorder was considered severe, and all patients improved after the infusion was decreased or stopped. One patient in the placebo group had an asthma attack within 15 days after the infusion. Two patients in the rituximab group and none in the placebo group developed purpura that was considered to be treatment-related within 15 days after an infusion. Rates of infection and severe infection were similar between groups (bronchitis and urinary and cutaneous infections were the more frequent manifestations in both groups), and no patients had opportunistic infections. In 2 patients receiving rituximab, cancer was diagnosed during routine investigations at 7 days (squamous cell carcinoma of the skin) and 38 days (breast cancer in a woman who died 1 year after inclusion) after enrollment. In 1 patient receiving placebo, superficial basal cell carcinoma was diagnosed 125 days after inclusion.

Table 1. **Baseline Characteristics of 120 Treated Patients**

Characteristic	Rituximab (*n* = 63)	Placebo (*n* = 57)
Mean (SD) age, *y*	52.9 (13.3)	55.6 (13.6)
Mean (SD) time since diagnosis, *y*	4.6 (4.8)	5.5 (6.5)
Mean (SD) time since first symptom, *y*	7.4 (5.8)	8.4 (7.6)
Women, *n (%)*	57 (90.5)	55 (96.5)
Mean (SD) VAS score, *mm*		
Global disease	68.9 (15.6)	69.4 (17.0)
Pain	49.7 (29.6)	57.5 (26.3)
Fatigue	70.9 (18.2)	66.9 (19.2)
Dryness	68.5 (23.1)	72.4 (18.1)
Mean (SD) dryness VAS score, *mm*		
Mouth	64.7 (24.8)	70.9 (23.4)
Eyes	61.4 (27.6)	60.5 (29.6)
Skin	48.8 (26.5)	54.7 (26.0)
Trachea	33.8 (29.0)	46.1 (31.9)
Ocular dryness, *n (%)*	60 (95.2)	51 (89.5)
Oral dryness, *n (%)*	63 (100)	55 (96.5)
Abnormal Schirmer test result, *n (%)*	34/39 (87.2)	28/36 (77.8)
Mean (SD) Schirmer test result, *mm*	11.3 (9.1)	11.5 (12.1)
Mean (SD) break-up time, *s*	5.4 (3.4)	5.9 (5.0)
Decreased salivary flow rate, *n (%)*	35/39 (89.7)	34/37 (91.9)
Mean (SD) salivary flow rate, *mL/min*	0.2 (0.4)	0.1 (0.1)
Focus score >1, *n (%)*	56 (88.9)	49 (86.0)
Anti-Ro/SSA or anti-La/SSB, *n (%)*	51 (81.0)	46 (80.7)
Hypergammaglobulinemia, *n (%)*	34 (54.0)	29 (50.9)
Mean (SD) immunoglobulin level, *g/L*	15.2 (5.1)	16.4 (7.8)
IgA	3.1 (1.9)	2.7 (1.3)
IgG	16.0 (5.7)	16.8 (8.0)
IgM	1.4 (0.7)	1.6 (2.6)
Mean (SD) SF-36 score		
PCS	37.5 (8.9)	34.9 (9.3)
MCS	36.5 (9.7)	36.5 (9.5)
Systemic signs, *n* (%)*		
Parotid gland enlargement	22 (34.9)	18 (31.6)
Pulmonary	7 (11.1)	9 (15.8)
Neurologic	9 (14.3)	8 (14.0)
Articular	19 (30.2)	14 (24.6)
Mean (SD) ESSDAI score	10.0 (6.9)	10.2 (6.8)
Mean (SD) physician-assessed global VAS score	56.7 (18.5)	55.4 (18.6)
Mean (SD) ESR, *mm/h*	27.9 (20.5)	30.4 (28.5)
Mean (SD) serum CRP level, *mg/L*	9.7 (20.0)	7.1 (9.6)
Steroid therapy, *n* (%)	17/53 (32.1)	17/47 (36.2)
Methotrexate, *n* (%)	10/53 (18.9)	7/47 (14.9)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ESSDAI = European League Against Rheumatism Sjögren Syndrome Disease Activity Index; MCS = Mental Component Summary subscore; PCS = Physical Component Summary subscore; SF-36 = Short Form-36 Health Survey; VAS = visual analogue scale.

* Included when prevalence was >5% of the total population as assessed by clinicians.

Table 2. **Comparison of Improvements in the Rituximab and Placebo Groups at Weeks 6, 16, and 24***

Variable	Week 6			
	Rituximab	Placebo	Difference (95% CI)	*P* Value
Patients with ≥30-mm improvement in VAS score, %†				
≥2 of 4 VASs‡	22.4	9.1	13.3 (0.8 to 25.8)	**0.036**
Global	15.8	8.0	7.8 (−8.6 to 24.1)	0.35
Pain	18.0	14.0	3.9 (−9.9 to 17.8)	0.57
Fatigue	34.7	8.2	26.6 (15.7 to 37.5)	**<0.001**
Dryness	16.6	8.6	8.0 (−3.7 to 19.7)	0.179
Mean improvement in ESSDAI score	0.8	1.0	−0.3 (−1.2 to 0.7)	0.60
Patients with physician-assessed improvements, %				
Disease activity	44.9	25.8	19.1 (4.4 to 33.7)	**0.011**
Systemic signs	7.8	18.0	−10.1 (−21.8 to 1.5)	0.089
Treatment efficacy	56.6	35.6	21.0 (9.3 to 32.7)	**0.001**
Mean improvements§				
Physician VAS, *mm*†	16.8	8.5	8.4 (4.2 to 12.5)	**<0.001**
Salivary flow rate, *mL/min*	0.01	0.02	−0.01 (−0.11 to 0.08)	0.80
Schirmer test result, *mm*	−0.4	−2.9	2.5 (0.0 to 5.0)	0.054
ESR, *mm/h*	2.4	2.8	−0.4 (−4.8 to 4.0)	0.84
Serum CRP level, *mg/L*	0.6	0.4	0.2 (−6.0 to 6.4)	0.95
IgG, *mg/L*	1.1	1.8	−0.7 (−2.3 to 0.9)	0.37
IgA, *mg/L*	0.3	−0.2	0.5 (0.1 to 1.0)	**0.026**
IgM, *mg/L*	0.2	0.0	0.2 (0.1 to 0.2)	**0.004**
C4 complement level, $g/L \times 10^{-4}$	0.0	−0.1	0.1 (−0.1 to 0.3)	0.32
β_2-Microglobulin level, $g/L \times 10^{-4}$	0.2	−0.2	0.4 (−0.4 to 1.1)	0.35
SF-36 score				
PCS	3.5	2.2	1.3 (−1.6 to 4.3)	0.36
MCS	5.1	2.8	2.2 (−2.5 to 6.9)	0.35

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ESSDAI = European League Against Rheumatism Sjögren Syndrome Disease Activity Index; MCS = Mental Component Summary subscore; PCS = Physical Component Summary subscore; SF-36 = Short Form-36 Health Survey; VAS = visual analogue scale.
* Statistically significant results are in bold.
† Scores range from 0 (none) to 100 mm (worst).
‡ Primary outcome at week 24.
§ Improvement is defined as a decrease from baseline to weeks 6, 16, and 24 for all variables except salivary flow rate, Schirmer test result, C4 complement level, β_2-microglobulin level, and SF-36 score.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, two 1-gram doses of rituximab given 2 weeks apart did not significantly increase the proportion of patients achieving the primary end point (≥30-mm decrease in ≥2 of 4 VAS scores at week 24). However, rituximab was associated with clinically significant improvements at week 6, suggesting transient efficacy that was not maintained throughout the 24-week period with our regimen. Fatigue was alleviated early, whereas effects on dryness were delayed. Thus, although our data provide some support for the efficacy of rituximab reported in 2 previous preliminary studies (10, 11), the size and duration of the benefit argue against treating pSS with rituximab.

Fatigue, which is a major source of disability in patients with pSS (24), was the symptom that responded best to rituximab therapy in our study. This cannot be ascribed to methylprednisolone treatment, which was identical in the 2 study groups. The VAS dryness score improved significantly among patients in the rituximab group, but by less than 30 mm. In the previous randomized, placebo-controlled trial, the stimulated total salivary flow rate was the primary outcome measure and was significantly improved by rituximab therapy (11); however, a baseline rate of at least 0.15 mL/min was an inclusion criterion. Whereas that trial (11) showed improvements in stimulated and unstimulated total salivary flow rates after 24 weeks of rituximab versus baseline, mean salivary flow rate was not improved in our rituximab group. Similarly, we found no effects of rituximab on other variables associated with dryness, such as the Schirmer test score for tear production or the Chisholm grade for salivary gland inflammation.

As assessed by using the ESSDAI, rituximab therapy had no significant effect on systemic pSS in our study. Similarly, the systemic signs assessed by the investigators did not improve in the rituximab group. The low baseline ESSDAI value may partially explain this result. Conversely, in a prospective cohort study of 28 patients with pSS (18), the ESSDAI score improved significantly with rituximab therapy and showed good external and internal validity.

The only adverse events seen more often with rituximab than placebo were infusion reactions within 24 hours

Table 2—**Continued**

Week 16				Week 24			
Rituximab	Placebo	Difference (95% CI)	*P* Value	Rituximab	Placebo	Difference (95% CI)	*P* Value
26.3	17.0	9.3 (−1.5 to 20.0)	0.091	23.0	22.0	1.0 (−16.7 to 18.7)	0.91
20.5	18.2	2.4 (−11.2 to 16.0)	0.73	16.9	24.0	−7.1 (−19.1 to 4.9)	0.25
15.2	15.9	−0.7 (−8.6 to 7.2)	0.86	12.6	22.0	−9.4 (−26.7 to 8.0)	0.29
27.2	8.9	18.3 (4.1 to 32.6)	**0.012**	20.1	10.8	9.3 (−2.0 to 20.5)	0.105
21.1	13.6	7.5 (−5.4 to 20.4)	0.25	25.6	13.2	12.4 (−3.0 to 27.8)	0.114
1.6	2.0	−0.3 (−1.7 to 1.0)	0.66	1.2	1.7	−0.5 (−2.3 to 1.3)	0.57
41.6	30.6	10.9 (−3.7 to 25.6)	0.142	44.6	43.3	1.4 (−15.3 to 18.0)	0.87
16.8	14.2	2.6 (−9.1 to 14.4)	0.66	18.4	22.7	−4.3 (−16.4 to 7.9)	0.48
53.6	52.8	0.8 (−8.6 to 10.2)	0.87	48.8	56.4	−7.6 (−20.0 to 4.8)	0.23
16.2	12.6	3.6 (−1.9 to 9.2)	0.20	15.0	10.9	4.1 (−1.6 to 9.8)	0.157
−0.01	−0.03	0.02 (−0.07 to 0.11)	0.69	0.01	−0.04	0.04 (−0.04 to 0.13)	0.29
−0.6	−1.4	0.7 (−2.7 to 4.2)	0.67	0.0	−1.9	1.9 (−0.2 to 4.1)	0.080
3.6	−0.9	4.5 (−1.7 to 10.7)	0.155	6.4	2.7	3.7 (−1.8 to 9.1)	0.185
3.0	1.9	1.1 (−2.5 to 4.7)	0.55	1.9	2.2	−0.3 (−2.3 to 1.6)	0.74
1.6	0.7	0.9 (0.1 to 1.8)	**0.021**	1.7	0.5	1.2 (0.4 to 2.0)	**0.003**
0.4	−0.1	0.4 (0.0 to 0.9)	0.063	0.4	−0.2	0.5 (0.0 to 1.1)	**0.047**
0.3	0.0	0.2 (0.1 to 0.3)	**<0.001**	0.3	0.0	0.3 (0.2 to 0.4)	**<0.001**
0.2	−0.1	0.3 (0.0 to 0.5)	**0.048**	0.2	0.1	0.1 (−0.2 to 0.4)	0.55
1.0	−0.5	1.5 (0.6 to 2.4)	**0.001**	1.0	−0.6	1.6 (0.5 to 2.8)	**0.004**
3.2	2.2	1.1 (−1.8 to 3.9)	0.46	3.8	3.2	0.6 (−1.5 to 2.6)	0.58
3.2	0.8	2.3 (−0.6 to 5.2)	0.116	1.7	1.2	0.5 (−2.9 to 4.0)	0.76

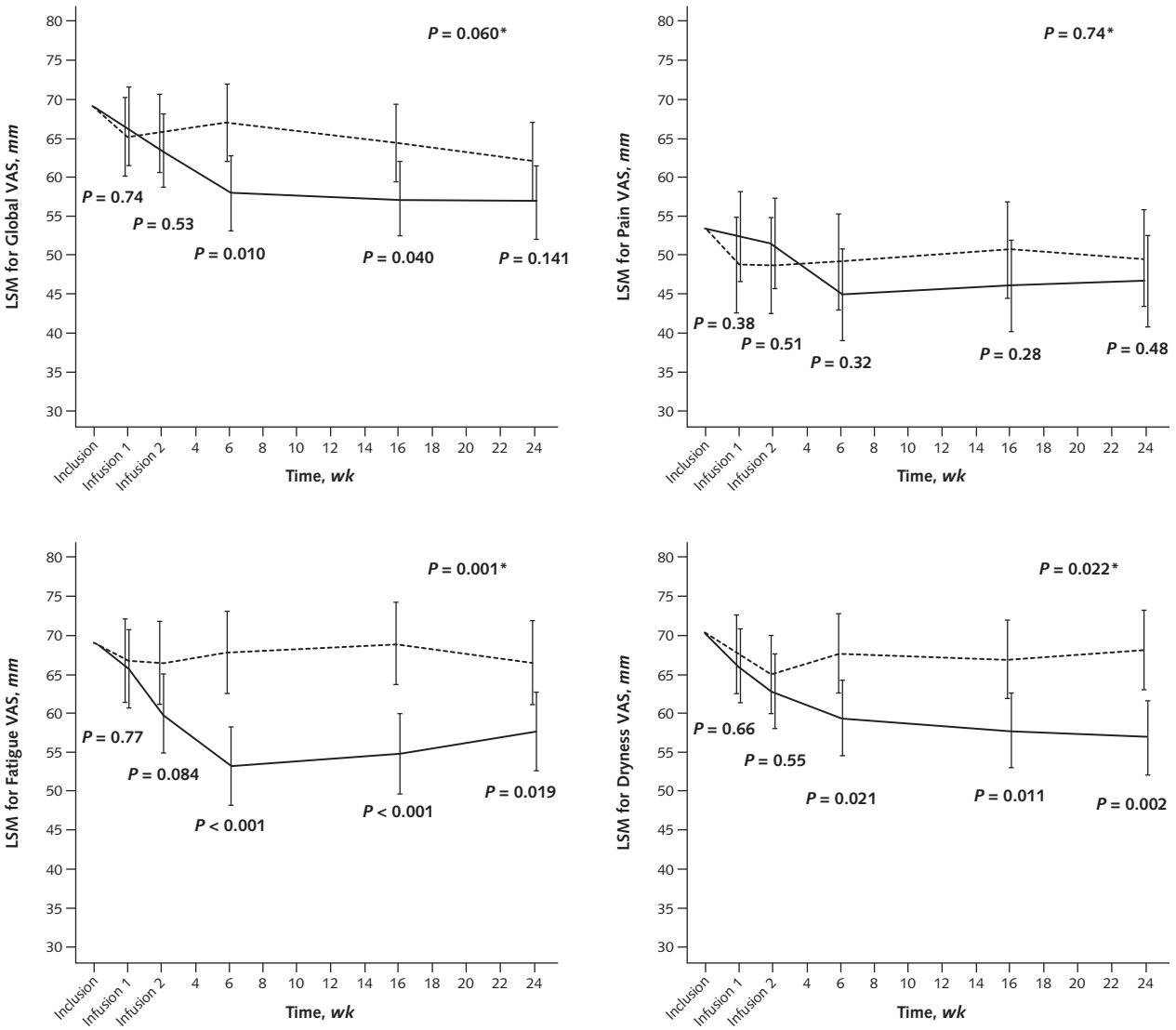
after an infusion. The occurrence of purpura in 2 patients who received rituximab was probably treatment-related. The difference in cutaneous adverse events between the groups was not significant, but this study was not powered to detect such a difference.

The timing of B-cell reconstitution is modulated by BAFF levels, and rituximab-induced B-cell depletion may result in decreased BAFF production (21). Serum BAFF levels were lower at week 24 than at baseline, but the difference was not statistically significant. Comparing serum BAFF levels at each time point to B-cell subsets in salivary gland infiltrates would be of interest because the results might help identify patients who are likely to respond. Similarly, the interferon response might help to predict the rituximab response because patients who do and do not respond to rituximab differ in the B-cell signaling pathway, extent of salivary gland infiltrates, and levels of interferon gene expression (25, 26).

In earlier studies, rituximab did not produce major therapeutic benefits in systemic lupus erythematosus, a disease whose pathophysiology largely depends on B cells (27). This finding suggests several points about the pathophysiologic process. First, plasmablasts have a long lifespan and exhibit limited susceptibility to rituximab, which may decrease the efficacy of rituximab therapy. Second, B cells in target organs, such as salivary glands, may show limited susceptibility to CD20 depletion. Finally, an imbalance between B cells and regulatory B cells in pSS may limit the therapeutic effects (28).

Our study has several limitations. First, the best outcome measure for assessing treatment efficacy in pSS is debatable. Clinical trials of potentially disease-modifying treatments in pSS have used various outcome measures (9, 10, 29–31). The earliest trial evaluating biological therapy for pSS used an improvement of at least 20% in 2 of 3 criteria (VAS scores or objective measures for oral and ocular dryness) and improvement in serum IgG level or erythrocyte sedimentation rate (30). Two recent, small, double-blind, placebo-controlled trials found that rituximab improved VAS scores for fatigue and dryness (10, 11). The ESSDAI (17), although validated to assess the activity of systemic pSS, was not selected in our study as the primary end point because we included patients without systemic manifestations. Given the high cost and po-

Figure 2. **LSMs and 95% CIs for VAS scores for global disease, pain, fatigue, and dryness after adjustment for baseline characteristics (mixed model) in the rituximab (*solid line*) and placebo (*dotted line*) groups.**



LSM = least-squares mean; VAS = visual analogue scale.
* Global *P* values are based on type III test evaluated with longitudinal regression analyses.

tential adverse effects of rituximab therapy, we chose a large effect as our primary outcome measure—namely, an improvement of at least 30 mm in at least 2 of 4 VAS scores evaluating different disease domains. This primary outcome may have been insensitive to detect clinically important changes in symptoms. Second, the best interval for assessing treatment efficacy in pSS is unclear. All previous studies on the biology of pSS evaluated the primary outcome between weeks 10 and 24. None of these studies suggested differences in treatment effects over time. We chose 24 weeks for our primary end point, an interval that seems consistent with the kinetics of rituximab's effects established in patients with rheumatoid arthritis. Third, patients had a low baseline activity score (mean ESSDAI score, 10.1), and we cannot exclude a better effect of the treatment in more active pSS. The study drug was prepared at hospital pharmacies in a manner that ensured blinding of the nurses, physicians, and patients. A few patients had infusion reactions, with no difference between the rituximab and placebo groups except for respiratory disorders and purpura. Therefore, the proportion of patients who may have guessed which treatment they received would have been small. In contrast, although corticosteroids given before infusions may modify the disease course over 1 month, the effect is probably not significant over a longer period.

Table 3. **Deaths, Adverse Events, Serious Adverse Events, and Discontinuations due to Adverse Events During the 24-Wk Study Period**

Variable	Patients, *n* (%)	
	Rituximab (*n* = 63)	Placebo (*n* = 57)
Death	0 (0)	0 (0)
Any adverse event	55 (87.3)	53 (93.0)
Infection	33 (52.4)	30 (52.6)
Any serious adverse event	13 (20.6)	8 (14.0)
Infection	2 (3.2)	5 (8.8)
Type of adverse event after first infusion*	5 (7.9)	1 (1.8)
Purpura†	1 (1.6)	–
Cytopenia‡	1 (1.6)	–
Allergy (cutaneous)†	1 (1.6)	–
Allergy (respiratory)†	1 (1.6)	–
Hyperglycemia†	1 (1.6)	–
Headache†	–	1 (1.8)

* These patients did not receive the second infusion.
† Adverse event.
‡ Serious adverse event.

In conclusion, our data do not support the use of rituximab therapy in many patients with recent-onset or systemic pSS. Nevertheless, rituximab induced several significant improvements in patients with recent-onset or systemic pSS. Fatigue was alleviated rapidly, whereas effects on dryness were delayed. The only adverse events seen more often with rituximab than placebo were infusion reactions within 24 hours after an infusion.

From Centre Hospitalier Universitaire de la Cavale Blanche, Université Bretagne Occidentale, Centre Hospitalier Universitaire Morvan, and Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique 0502, Centre Hospitalier Universitaire Brest, Brest, France; Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Institut National de la Santé et de la Recherche Médicale U1012, Université Paris-Sud, Le Kremlin Bicêtre; Hôtel-Dieu, Centre Hospitalier Universitaire Nantes, Nantes; Centre Hospitalier Universitaire Hôpital Sud, Rennes; Centre Hospitalier du Mans, Le Mans; Hopital Cochin and Hôpital Bichat, Paris; Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg; Hôpital de la Conception, Marseille; Claude Huriez Hospital, Lille2 University, Lille; Centre Hospitalier de Rouen, Bois-Guillaume; Centre Hospitalier Universitaire Lapeyronie, Montpellier; Centre Hospitalier Monod, Montivilliers; Gabriel Montpied Teaching Hospital, Place H. Dunant, Clermont-Ferrand.

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Requests for Single Reprints: Alain Saraux, MD, PhD, Rheumatology Unit, Hôpital de la Cavale Blanche, BP 824, F 29609 Brest Cedex, France; e-mail, alain.saraux@chu-brest.fr.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Devauchelle-Pensec, Jousse-Joulin, and Saraux: Service de Rhumatologie, Centre Hospitalier Universitaire de la Cavale Blanche, Boulevard Tanguy Prigent, 29609 Brest, France.
Dr. Mariette: Service de Rhumatologie, Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, 78 Rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France.
Dr. Berthelot: Service de Rhumatologie, Hôtel-Dieu, Centre Hospitalier Universitaire Nantes, 44093, Nantes Cedex 01, France.
Dr. Perdriger: Service de Rhumatologie, Centre Hospitalier Universitaire Hôpital Sud, 35 000 Rennes, France.
Drs Puéchal and Le Guern: National Referral Center for Rare Systemic Autoimmune Diseases, 27 Rue du Faubourg Saint Jacques, 75014 Cochin Hospital, France.
Drs. Sibilia and Gottenberg: Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, 1 Avenue Molière, 67098 Strasbourg Cedex, France.
Dr. Chiche: Service de Médecine Interne, Hôpital de la Conception, 147 Boulevard Baille, 13005 Marseille, France.
Drs. Hachulla and Hatron: Department of Internal Medicine, Claude Huriez Hospital, Lille2 University, 59037 Lille Cedex, France.
Dr. Goeb: Service de Rhumatologie, Centre Hospitalier Universitaire d'Amiens, Place Victor Pauchet 80054 Amiens Cedex 1, France.
Dr. Hayem: Service de Rhumatologie, Hôpital Bichat, 46 Rue Henri Huchard, 75877 Paris Cedex 18, France.
Dr. Morel: Service d'Immuno-Rhumatologie, Centre Hospitalier Universitaire Lapeyronie, 34 295 Montpellier, France.
Dr. Zarnitsky: Service de Rhumatologie, Centre Hospitalier Monod, Montivilliers, France.
Dr. Dubost: Rheumatology Department, Gabriel Montpied Teaching Hospital, Place H. Dunant, Clermont-Ferrand 63000, France.
Dr. Pers: Odontology, Centre Hospitalier Universitaire Morvan, 29609 Brest, France and EA 2216, Université Bretagne Occidentale, 29200 Brest, France.
Dr. Nowak: Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique 0502, Centre Hospitalier Universitaire de la Cavale Blanche, Boulevard Tanguy Prigent, 29609 Brest, France.

Author Contributions: Conception and design: V. Devauchelle-Pensec, X. Mariette, S. Jousse-Joulin, X. Puéchal, V. Le Guern, J. Sibilia, J.E. Gottenberg, J.O. Pers, E. Nowak, A. Saraux.
Analysis and interpretation of the data: V. Devauchelle-Pensec, X. Mariette, S. Jousse-Joulin, J. Sibilia, J.E. Gottenberg, L. Chiche, E. Hachulla, J.O. Pers, E. Nowak, A. Saraux.
Drafting of the article: V. Devauchelle-Pensec, X. Mariette, J. Sibilia, L. Chiche, E. Nowak, A. Saraux.
Critical revision of the article for important intellectual content: V. Devauchelle-Pensec, X. Mariette, J.M. Berthelot, J. Sibilia, J.E. Gottenberg, E. Hachulla, J.O. Pers, A. Saraux.
Final approval of the article: V. Devauchelle-Pensec, X. Mariette, S. Jousse-Joulin, A. Perdriger, X. Puéchal, V. Le Guern, J. Sibilia, J.E. Gottenberg, L. Chiche, E. Hachulla, P.Y. Hatron, V. Goeb, G. Hayem, J. Morel, J.J. Dubost, J.O. Pers, E. Nowak, A. Saraux.
Provision of study materials or patients: V. Devauchelle-Pensec, X. Mariette, S. Jousse-Joulin, J.M. Berthelot, X. Puéchal, V. Le Guern, J.E. Gottenberg, L. Chiche, E. Hachulla, P.Y. Hatron, V. Goeb, G. Hayem, J. Morel, C. Zarnitsky, A. Saraux.
Statistical expertise: V. Devauchelle-Pensec, E. Nowak, A. Saraux.
Obtaining of funding: A. Saraux.
Administrative, technical, or logistic support: V. Devauchelle-Pensec, L. Chiche, V. Goeb, A. Saraux.
Collection and assembly of data: V. Devauchelle-Pensec, X. Mariette, J.M. Berthelot, A. Perdriger, X. Puéchal, V. Le Guern, J. Sibilia, J.E. Gottenberg, L. Chiche, E. Hachulla, V. Goeb, J.J. Dubost, A. Saraux.

Appendix Table 1. **Sensitivity Analyses: Percentage of Patients With ≥30-mm Improvement for Each VAS and for ≥2 of 4 VASs***

Analysis	Week 6				Week 16				Week 24			
	Rituximab, %	Placebo, %	Absolute Difference (95% CI), *percentage points*	*P* Value	Rituximab, %	Placebo, %	Absolute Difference (95% CI), *percentage points*	*P* Value	Rituximab, %	Placebo, %	Absolute Difference (95% CI), *percentage points*	*P* Value
≥2 of 4 VASs†												
Multiple imputation (primary analysis)	22.4	9.1	13.3 (0.8 to 25.8)	**0.036**	26.3	17.0	9.3 (−1.5 to 20.0)	0.091	23.0	22.0	1.0 (−16.7 to 18.7)	0.91
Missing data regarded as nonresponse to treatment	19.1	7.1	12.1 (0.2 to 23.9)	**0.047**	23.9	15.7	8.2 (−1.1 to 17.5)	0.082	21.5	20.5	1.0 (−15.1 to 17.2)	0.90
Available data	20.4	7.3	13.1 (0.0 to 25.8)	**0.045**	25.6	16.4	9.3 (0.0 to 19.1)	0.064	21.9	20.9	1.0 (−16.1 to 18.2)	0.91
Global VAS												
Multiple imputation (primary analysis)	15.8	8.0	7.8 (−8.6 to 24.1)	0.35	20.5	18.2	2.4 (−11.2 to 16.0)	0.73	16.9	24.0	−7.1 (−19.1 to 4.9)	0.25
Missing data regarded as nonresponse to treatment	13.3	6.2	7.1 (−8.9 to 23.0)	0.39	18.5	16.6	1.9 (−11.3 to 15.1)	0.78	14.6	21.3	−6.7 (−17.0 to 3.5)	0.199
Available data	13.9	6.0	7.9 (−9.3 to 25.1)	0.37	20.4	17.4	2.9 (−10.6 to 16.5)	0.67	15.6	22.8	−7.2 (−18.2 to 3.7)	0.195
Pain VAS												
Multiple imputation (primary analysis)	18.0	14.0	3.9 (−9.9 to 17.8)	0.57	15.2	15.9	−0.7 (−8.6 to 7.2)	0.86	12.6	22.0	−9.4 (−26.7 to 8.0)	0.29
Missing data regarded as nonresponse to treatment	15.9	12.4	3.6 (−9.7 to 16.8)	0.60	14.3	15.7	−1.5 (−9.5 to 6.5)	0.71	11.6	21.5	−9.8 (−26.6 to 6.9)	0.25
Available data	16.8	12.8	3.9 (−9.8 to 17.7)	0.58	15.2	16.3	−1.1 (−9.0 to 6.8)	0.79	11.4	21.4	−10.0 (−27.2 to 7.3)	0.26
Fatigue VAS												
Multiple imputation (primary analysis)	34.7	8.2	26.6 (15.7 to 37.5)	**<0.001**	27.2	8.9	18.3 (4.1 to 32.6)	**0.012**	20.1	10.8	9.3 (−2.0 to 20.5)	0.105
Missing data regarded as nonresponse to treatment	33.0	6.9	26.1 (15.5 to 36.6)	**<0.001**	26.5	8.6	17.9 (5.2 to 30.5)	**0.006**	17.3	8.7	8.6 (−2.2 to 19.5)	0.119
Available data	34.4	7.0	27.4 (17.0 to 37.8)	**<0.001**	27.8	8.7	19.2 (5.7 to 32.6)	**0.005**	18.2	9.2	9.0 (−2.1 to 20.2)	0.113
Dryness VAS												
Multiple imputation (primary analysis)	16.6	8.6	8.0 (−3.7 to 19.7)	0.179	21.1	13.6	7.5 (−5.4 to 20.4)	0.25	25.6	13.2	12.4 (−3.0 to 27.8)	0.114
Missing data regarded as nonresponse to treatment	13.3	7.9	5.5 (−3.7 to 14.6)	0.24	21.3	13.3	8.0 (−3.8 to 19.8)	0.183	24.1	10.8	13.3 (0.0 to 26.5)	0.051
Available data	13.5	7.8	5.7 (−3.9 to 15.3)	0.24	21.5	13.0	8.5 (−3.9 to 20.9)	0.180	25.2	11.5	13.7 (−1.2 to 28.5)	0.071

VAS = visual analogue scale.
* Statistically significant results are in bold.
† Primary outcome at week 24.

Appendix Table 2. **Disease Activity in Each ESSDAI Domain in the Rituximab and Placebo Groups at Weeks 6, 16, and 24***

Domain	Baseline		Week 6		Week 16		Week 24	
	Rituximab (*n* = 63)	**Placebo (*n* = 57)**	**Rituximab (*n* = 61)**	**Placebo (*n* = 56)**	**Rituximab (*n* = 60)**	**Placebo (*n* = 55)**	**Rituximab (*n* = 61)**	**Placebo (*n* = 54)**
Constitutional	None: 47 Low: 5 Moderate: 11	None: 41 Low: 4 Moderate: 12	None: 51 Low: 0 Moderate: 10	None: 45 Low: 0 Moderate: 11	None: 48 Low: 1 Moderate: 11	None: 41 Low: 0 Moderate: 14	None: 48 Low: 2 Moderate: 11	None: 41 Low: 0 Moderate: 13
Lymphadenopathy	None: 59 Low: 3 Moderate: 1	None 54 Low: 3 Moderate: 0	None: 57 Low: 4 Moderate: 0	None: 54 Low: 2 Moderate: 0	None: 58 Low: 2 Moderate: 0	None: 54 Low: 0 Moderate: 1	None: 58 Low: 2 Moderate: 1	None: 52 Low: 2 Moderate: 0
Glandular	None: 45 Low: 10 Moderate: 8	None: 42 Low: 6 Moderate: 9	None: 44 Low: 13 Moderate: 4	None: 40 Low: 12 Moderate: 4	None: 47 Low: 11 Moderate: 2	None: 42 Low: 9 Moderate: 4	None: 47 Low: 9 Moderate: 5	None: 40 Low: 8 Moderate: 6
Articular	None: 33 Low: 12 Moderate: 13 High: 5	None: 30 Low: 14 Moderate: 9 High: 4	None: 33 Low: 12 Moderate: 13 High: 3	None: 31 Low: 16 Moderate: 7 High: 2	None: 33 Low: 17 Moderate: 8 High: 2	None: 31 Low: 16 Moderate: 6 High: 2	None: 36 Low: 16 Moderate: 5 High: 4	None: 32 Low: 14 Moderate: 4 High: 4
Cutaneous	None: 58 Low: 1 Moderate: 2 High: 2	None: 55 Low: 0 Moderate: 1 High: 1	None: 59 Low: 0 Moderate: 1 High: 1	None: 54 Low: 0 Moderate: 1 High: 1	None: 59 Low: 0 Moderate: 1 High: 0	None: 53 Low: 0 Moderate: 0 High: 2	None: 59 Low: 0 Moderate: 2 High: 0	None: 53 Low: 0 Moderate: 0 High: 1
Pulmonary	None: 52 Low: 10 Moderate: 1	None: 40 Low: 11 Moderate: 6	None: 49 Low: 11 Moderate: 1	None: 40 Low: 12 Moderate: 4	None: 49 Low: 11 Moderate: 0	None: 44 Low: 9 Moderate: 2	None: 49 Low: 11 Moderate: 1	None: 43 Low: 8 Moderate: 3
Renal	None: 57 Low: 1 Moderate: 0 High: 5	None: 56 Low: 0 Moderate: 0 High: 1	None: 55 Low: 1 Moderate: 0 High: 5	None: 55 Low: 0 Moderate: 0 High: 1	None: 55 Low: 1 Moderate: 0 High: 4	None: 55 Low: 0 Moderate: 0 High: 0	None: 55 Low: 1 Moderate: 0 High: 5	None: 53 Low: 0 Moderate: 0 High: 1
Muscular	None: 61 Low: 1 Moderate: 1	None: 56 Low: 1 Moderate: 0	None: 59 Low: 1 Moderate: 1	None: 55 Low: 1 Moderate: 0	None: 58 Low: 1 Moderate: 1	None: 54 Low: 1 Moderate: 0	None: 59 Low: 1 Moderate: 1	None: 53 Low: 1 Moderate: 0
PNS	None: 54 Low: 4 Moderate: 4 High: 1	None: 47 Low: 2 Moderate: 8 High: 0	None: 52 Low: 3 Moderate: 6 High: 0	None: 46 Low: 2 Moderate: 8 High: 0	None: 51 Low: 4 Moderate: 5 High: 0	None: 46 Low: 2 Moderate: 7 High: 0	None: 51 Low: 7 Moderate: 3 High: 0	None: 46 Low: 3 Moderate: 5 High: 0
CNS	None: 63 Low: 0 Moderate: 0	None: 57 Low: 0 Moderate: 0	None: 61 Low: 0 Moderate: 0	None: 56 Low: 0 Moderate: 0	None: 60 Low: 0 Moderate: 0	None: 55 Low: 0 Moderate: 0	None: 61 Low: 0 Moderate: 0	None: 54 Low: 0 Moderate: 0
Hematologic	None: 39 Low: 22 Moderate: 2	None: 34 Low: 18 Moderate: 5	None: 34 Low: 22 Moderate: 5	None: 35 Low: 18 Moderate: 3	None: 33 Low: 22 Moderate: 5	None: 35 Low: 16 Moderate: 4	None: 36 Low: 22 Moderate: 3	None: 34 Low: 17 Moderate: 3
Biological	None: 27 Low: 19 Moderate: 17	None: 24 Low: 15 Moderate: 18	None: 32 Low: 12 Moderate: 17	None: 25 Low: 13 Moderate: 18	None: 30 Low: 9 Moderate: 21	None: 22 Low: 16 Moderate: 17	None: 29 Low: 12 Moderate: 20	None: 20 Low: 17 Moderate: 17

CNS = central nervous system; ESSDAI = European League Against Rheumatism Sjögren Syndrome Disease Activity Index; PNS = peripheral nervous system.

Appendix Table 3. **Adverse Events and Serious Adverse Events During the 24-Wk Study Period and Postinfusion Periods**

System Organ Class	Patients With Adverse Event (Serious Adverse Event), *n*					
	During Study Period		Within 15 d of Infusion		Within 24 h of Infusion	
	Rituximab (*n* = 63)	Placebo (*n* = 57)	Rituximab (*n* = 63)	Placebo (*n* = 57)	Rituximab (*n* = 63)	Placebo (*n* = 57)
General disorders and administration site conditions	11 (2)	12 (0)	7 (1)	12 (0)	6 (0)	10 (0)
Skin and subcutaneous tissue disorders	15 (3)	12 (0)	10 (3)	9 (0)	4 (1)	6 (0)
Nervous system disorders	14 (1)	9 (0)	11 (0)	7 (0)	4 (0)	5 (0)
Respiratory, thoracic, and mediastinal disorders	8 (1)	8 (1)	7* (1)	1 (0)	7† (1)	0 (0)
Gastrointestinal disorders	19 (0)	16 (0)	8 (0)	5 (0)	3 (0)	2 (0)
Infections and infestations	33 (2)	30 (5)	10 (0)	5 (0)	3 (0)	2 (0)
Vascular disorders	6 (1)	6 (0)	2 (0)	3 (0)	2 (0)	3 (0)
Musculoskeletal and connective tissue disorders	18 (1)	11 (0)	2 (0)	7 (0)	0 (0)	3 (0)
Blood and lymphatic system disorders	3 (2)	3 (0)	3 (1)	1 (0)	1 (0)	1 (0)
Ear and labyrinth disorders	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine disorders	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders	3 (0)	2 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Immune system disorders	2 (1)	1 (0)	2 (0)	0 (0)	1 (0)	0 (0)
Psychiatric disorders	3 (0)	1 (0)	1 (0)	1 (0)	0 (0)	1 (0)
Renal and urinary	0 (0)	3 (1)	0 (0)	1 (0)	0 (0)	0 (0)
Benign, malignant, or unspecified neoplasm	2 (2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Surgical and medical procedures	5 (1)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive and breast disorders	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oral fungal infection	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injury, poisoning, or procedural complications	5 (0)	4 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders	3 (1)	1 (1)	1 (0)	0 (0)	1 (0)	0 (0)
Total	55 (13)	53 (8)	41 (5)	37 (0)	27 (2)	26 (0)

* $P = 0.064$ (Fisher exact test).
† $P = 0.014$ (Fisher exact test).