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Development of the Sjögren's Syndrome Responder Index, a data-driven composite endpoint for assessing treatment efficacy

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Abstract

Objectives. To determine which outcome measures detected rituximab efficacy in the Tolerance and Efficacy of Rituximab in Sjo¨gren's Disease (TEARS) trial and to create a composite endpoint for future trials in primary SS (pSS).

Methods. Post hoc analysis of the multicentre randomized placebo-controlled double-blind TEARS trial. The results were validated using data from two other randomized controlled trials in pSS, assessing rituximab (single-centre trial in the Netherlands) and infliximab, respectively.

Results. Five outcome measures were improved by rituximab in the TEARS trial: patient-assessed visual analogue scale scores for fatigue, oral dryness and ocular dryness, unstimulated whole salivary flow and ESR. We combined these measures into a composite endpoint, the SS Responder Index (SSRI), and we defined an SSRI-30 response as a 530% improvement in at least two of five outcome measures. In TEARS, the proportions of patients with an SSRI-30 response in the rituximab and placebo groups at 6, 16 and 24 weeks were 47% vs 21%, 50% vs 7% and 55% vs 20%, respectively ($P < 0.01$ for all comparisons). SSRI-30 response rates after 12 and 24 weeks in the single-centre rituximab trial were 68% (13/19) vs 40% (4/10) and 74% (14/19) vs 40% (4/10), respectively. No significant differences in SSRI-30 response rates were found between infliximab and placebo at any of the time points in the infliximab trial.

Conclusion. A core set of outcome measures used in combination suggests that rituximab could be effective and infliximab ineffective in pSS. The SSRI might prove useful as the primary outcome measure for future therapeutic trials in pSS.

Key words: primary Sjö¨gren's syndrome, rituximab, efficacy, outcome measures

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Rheumatology key messages

- The absence of positive trials in pSS may be due to the absence of validated endpoints.
- The tolerance and efficacy of rituximab in SS trial data give the unique opportunity to study the sensitivity to change in outcome measures.
- We developed the Sjögren's Syndrome Responder Index, a data-driven composite endpoint, to be used in future primary SS trials.

Introduction

Primary SS (pSS) is a systemic autoimmune disease, with an estimated prevalence of 40 patients per 100 000 inhabitants in Europe [1]. The hallmark of pSS is infiltration of the salivary and lachrymal glands by inflammatory cells. The predominant symptoms consist of ocular and oral dryness, severe fatigue and widespread pain, which severely impair health-related quality of life. Systemic involvement may develop, causing life-threatening manifestations in some patients.

The current management of pSS relies largely on the routine prescription of symptomatic treatments. Immunosuppressive drugs are used in patients with severe systemic involvement, despite the paucity of evidence supporting this practice [2]. Research into the pathophysiology of pSS has established a central role for B cells [3], suggesting possible therapeutic efficacy of B cell targeting agents [4]. Several open-label studies and two small randomized trials [5–9] have suggested that B cell depletion by rituximab may improve the symptoms and lessen the systemic activity of pSS. TRACTISS (Trial of Anti-B-Cell Therapy in Patients With Primary Sjögren's Syndrome) is a large randomized placebo-controlled trial of rituximab that is under way in the UK [10]. Another randomized placebo-controlled trial of rituximab—Tolerance and Efficacy of Rituximab in Sjögren's Disease (TEARS)—was conducted in France and the results published recently [11]. The primary endpoint was a 530 mm improvement at week 24 in at least two of four patient-assessed 100 mm visual analogue scales (VASs) assessing global disease, pain, fatigue and dryness. The proportion of patients achieving this primary endpoint was not significantly different between the rituximab and placebo groups after 6 months. However, several secondary endpoints were significantly improved by rituximab compared with placebo.

The best means of assessing treatment efficacy in pSS is highly controversial. Given the subjective nature of many pSS symptoms and the marked health-related quality of life impairments induced by the disease, patient-assessed VAS scores for various manifestations are widely used in clinical research on pSS. However, the best assessment time points and the degree of VAS score improvement that is clinically relevant remain unclear. An additional challenge arises from the marked clinical heterogeneity of pSS. The EULAR SS Patient-Reported Index (ESSPRI) and the EULAR SS Disease Activity Index (ESSDAI) are recently developed composite indices that assess subjective symptoms and systemic disease activity, respectively [12–15]. However, neither of these tools has been used as the primary endpoint in a large therapeutic trial in pSS. Thus an important goal of current research into pSS is the development of a tool for assessing treatment efficacy.

Here our objective was to develop a composite index capable of detecting therapeutic responses in patients with pSS, and therefore potentially useful in future clinical trials. To this end, we conducted a post hoc analysis of data from the TEARS trial. We then applied the new index to data from two other published randomized controlled trials in pSS, a multicentre study of infliximab and a single-centre study of rituximab. In addition, we evaluated the ability of the ESSPRI and ESSDAI to detect therapeutic effects in the TEARS study.

Patients and methods

Patients

The TEARS study included 120 patients between 2008 and 2011 [11]. Patients were required to meet American–European Consensus Group (AECG) pSS classification criteria [16] and to have scores of 550 mm on at least two of four 100 mm VASs for global disease activity, pain, fatigue and dryness. Patients could have either symptom onset within the past 10 years with current laboratory evidence of active disease or systemic disease defined as at least one extraglandular manifestation. The patients were allocated at random to rituximab (two 1000 mg i.v. infusions 2 weeks apart, n = 63) or placebo (n = 57). All patients received 100 mg of methylprednisolone intravenously and 500 mg of acetaminophen orally before each placebo or rituximab infusion. Women comprised 91.8% of the population and the mean age was 54.3 years (S.D. 13.7). Of the 120 patients, 64 (53%) had a Schirmer's test 45 mm/5 min, 71 (59%) had an unstimulated whole saliva flow (UWSF) 40.1 ml/min, 97 (80.8%) had positive tests for anti-SSA/SSB antibodies and 105 (87.5%) had a labial salivary gland focus score 51. The TEARS study was approved by the appropriate ethics committee (CPP Ouest VI, 2007/493) and all patients gave their written informed consent before study inclusion. The protocol of the TEARS study was registered on clinicaltrials.gov (NCT00740948). No supplemental ethics committee approval was required for these post hoc analyses.

In 2010, Meijer et al. [9] reported a single-centre randomized trial conducted in the Netherlands to compare two 1000-mg rituximab infusions (n = 20) and a placebo (n = 10) in patients with pSS. Inclusion criteria were fulfilment of AECG criteria for pSS, stimulated whole saliva flow 50.15 ml/min, positive tests for RF and anti-SSA antibodies and abnormal salivary gland histology.

Follow-up was 48 weeks. The protocol was registered on clinicaltrials.gov (NCT00363350).

Finally, the multicentre TRIPSS study, published in 2004, compared infliximab with a placebo in 103 patients fulfilling AECG criteria for pSS [17]. Three infliximab infusions (5 mg/kg at weeks 0, 2 and 6) were compared with a placebo. Follow-up was 22 weeks.

Outcome measures

TEARS study participants were evaluated at baseline and weeks 6, 16 and 24. At each visit they used 100 mm VASs to evaluate global disease activity; limb pain; fatigue; and global, oral, ocular, vaginal and skin dryness. They were also questioned at each visit on global health improvement from baseline (i.e. responded yes or no to the question, Do you think that your global health status improved since you started this study?) and whether this improvement was due to the study medication; they also filled out a 36-item short form quality of life scale. In addition, at each visit the physician used 100 mm VASs to assess global disease activity and systemic disease activity and obtained the following objective measurements: Schirmer's test, van Bijsterveld score (at week 24 only), UWSF, ESR and b_2 microglobulin. According to the demonstrated effect of rituximab on immunoglobulin levels irrespective of clinical efficacy, we did not include them in our analyses. The ESSPRI (mean of 100-mm VAS scores for limb pain, fatigue and global dryness) at each visit was computed retrospectively. The final version of the ESSDAI (measuring systemic disease activity in 12 weighted domains, with a total score range of 0- 123) was not available at study initiation but was computed retrospectively for each patient (the different components of the ESSDAI were prospectively collected during the trial as several investigators were involved in the development of the score).

Statistical analysis

We determined which TEARS outcome measures improved with rituximab therapy. For each measure, absolute improvement was computed as the difference between baseline and post-treatment values and relative improvement (%) as the absolute improvement divided by the baseline value. Improvements were increases for Schirmer's test and UWSF and decreases for all other measures.

Correlations between improvements in VAS oral and ocular dryness scores at each visit were evaluated using Spearman's rank correlation coefficient () to determine whether improvements were greater for global dryness or for separate assessments of oral and ocular dryness.

We defined cut-offs for each outcome measure to separate responders and non-responders. For absolute improvements, the arbitrarily chosen cut-offs indicating small, moderate, marked and very marked improvements were 10, 20, 30 and 40 mm decreases in VAS scores vs baseline, respectively; 1, 2, 3 and 4 point decreases in the van Bijsterveld score, respectively; 1, 2, 5 and 10 mm/5 min increases in Schirmer's test, respectively; 0.01, 0.03, 0.06 and 0.1 ml/min increases in UWSF, respectively; 5, 10, 15 and 20 mm/h decreases in ESR, respectively; and 0.1, 0.2, 0.3 and 0.4 IU decreases in b_2 microglobulin, respectively. Small, moderate, marked and very marked relative improvements were defined as changes by 10%, 20%, 30%, and 40% vs baseline, respectively. We used all available data; patients with missing data for an outcome measure were excluded from the analysis of that measure.

We arbitrarily assumed that a 20% difference in response between the rituximab and placebo groups was the minimal relevant difference and that a good outcome measure should detect such a difference using several cut-offs to define improvement. We then identified the outcome measures showing a 520% between-group difference using at least two different cut-offs at a given visit, and we combined them into a composite endpoint, which we designated the SS Responder Index (SSRI). At each time point we used various definitions of a response to assess each SSRI component separately and combinations of one, two, three or more than three SSRI components. We compared SSRI values with ESSPRI and ESSDAI values in the TEARS study.

We then applied the SSRI to the data from two other published randomized controlled trials in pSS, a single-centre study of rituximab and a multicentre study of infliximab [9, 17]. All statistical tests were performed using SPSS for Windows version 20.0 (IBM, Armonk, NY, USA).

Results

Absolute vs relative improvements

Relative improvements in the TEARS study are reported in Table 1 and absolute improvements are reported in supplementary Table S1, available at Rheumatology Online. These two methods yielded similar results overall, although relative improvements showed larger between-group differences and greater consistency across cut-offs. Consequently, further analyses were confined to relative improvements.

Oral and ocular dryness improvements assessed using VAS scores were moderately correlated (= 0.469, 0.478 and 0.446 at weeks 6, 16 and 24, respectively). We therefore performed separate assessments of VAS ocular and oral dryness scores.

Analysis and selection of single outcome measures

In the TEARS study, rituximab improved physician-assessed global and systemic activity only at week 16 and the between-group differences were small for both measures (Table 1). The VAS fatigue score was improved significantly more often by rituximab than placebo at weeks 6 and 16, but not at week 24. The VAS oral dryness score was better with rituximab at all three time points and the VAS ocular dryness score at the 16 and 24 week time points. Rituximab was not significantly better than the placebo in improving the other patient-reported outcomes (global disease activity, limb pain, skin dryness and vaginal dryness).

TABLE 1 Comparison of the rates of relative improvement between the rituximab and placebo groups

	10% improvement			20% improvement			30% improvement			40% improvement		
Outcome measure	RTX	PBO	P-value	RTX	PBO	P-value	RTX	PBO	P-value	RTX	PBO	P-value
Week 6												
Global activity physician	63 (38/60)	52 (29/56)	0.208	52 (31/60)	39 (22/56)	0.181	43 (26/60)	32 (18/56)	0.215	32 (19/60)	25 (14/56)	0.426
Systemic activity physician	58 (35/60)	45 (25/56)	0.140	53 (32/60)	39 (22/56)	0.130	40 (24/60)	32 (18/56)	0.379	35 (21/60)	27 (15/56)	0.339
Schirmer's test	29 (17/58)	25 (13/52)	0.612	26 (15/58)	23 (12/52)	0.735	17 (10/58)	19 (10/52)	0.787	17 (10/58)	17 (9/52)	0.993
UWSF	50 (26/52)	31 (15/49)	0.047	46 (24/52)	31 (15/49)	0.109	40 (21/52)	27 (13/49)	0.141	38 (20/52)	22 (11/49)	0.081
ESR	52 (29/56)	35 (18/51)	0.086	30 (17/56)	22 (11/51)	0.302	32 (13/56)	18 (9/51)	0.477	16 (9/56)	10 (5/51)	0.337
b_2 microglobulin	20 (10/49)	10 (5/49)	0.161	8 (4/49)	2 (1/49)	0.362	2 (1/49)	0 (0/49)	1	0	0	
Global activity patient	50 (29/58)	36 (20/55)	0.144	36 (21/58)	25 (14/55)	0.217	26 (15/58)	15 (8/55)	0.135	19 (11/58)	11 (6/55)	0.231
Pain	47 (28/60)	49 (27/55)	0.795	38 (23/60)	35 (19/55)	0.673	32 (19/60)	25 (14/55)	0.462	30 (18/60)	20 (11/55)	0.217
Fatigue	55 (33/60)	36 (20/55)	0.045	48 (29/60)	25 (14/55)	0.011	42 (25/60)	20 (11/55)	0.012	40 (24/60)	9 (5/55)	<0.001
Oral dryness	56 (32/57)	26 (14/53)	0.002	44 (25/57)	15 (8/53)	0.001	32 (18/57)	11 (6/53)	0.01	25 (14/57)	9 (5/53)	0.036
Ocular dryness	46 (26/57)	33 (18/54)	0.186	26 (15/57)	17 (9/54)	0.217	16 (9/57)	13 (7/54)	0.672	16 (9/57)	4 (2/54)	0.054
Skin dryness	47 (27/57)	41 (22/54)	0.482	46 (26/57)	28 (15/54)	0.052	30 (17/57)	19 (10/54)	0.165	21 (12/57)	15 (8/54)	0.393
Vaginal dryness	56 (29/52)	39 (20/51)	0.094	42 (22/52)	31 (16/51)	0.205	42 (22/52)	29 (15/51)	0.139	38 (20/52)	25 (13/51)	0.180
Week 16												
Global activity physician	69 (40/58)	53 (29/55)	0.077	59 (34/58)	38 (21/55)	0.030	48 (28/58)	33 (18/55)	0.093	36 (21/58)	24 (13/55)	0.145
Systemic activity physician	59 (34/58)	49 (27/55)	0.310	57 (33/58)	38 (21/55)	0.047	43 (25/58)	33 (18/55)	0.256	31 (18/58)	31 (17/55)	0.989
Schirmer's test	23 (12/53)	25 (13/52)	0.777	21 (11/53)	23 (12/52)	0.774	19 (10/53)	21 (11/52)	0.77	15 (8/53)	19 (10/52)	0.574
UWSF	33 (17/50)	21 (10/48)	0.145	32 (16/50)	21 (10/48)	0.211	32 (16/50)	21 (10/48)	0.211	30 (15/50)	19 (9/48)	0.195
ESR	63 (33/52)	33 (16/49)	0.002	56 (29/52)	20 (10/49)	<0.001	37 (19/52)	10 (5/49)	0.002	31 (16/52)	8 (4/49)	0.004
b_2 microglobulin	24 (12/49)	9 (4/46)	0.040	8 (4/49)	2 (1/45)	0.363	6 (3/49)	0 (0/46)	0.243	0	0	
Global activity patient	53 (31/58)	36 (20/55)	0.068	45 (26/58)	29 (16/55)	0.084	33 (19/58)	20 (11/55)	0.125	24 (1/58)	16 (9/55)	0.305
Pain	46 (27/59)	36 (20/55)	0.308	34 (20/59)	29 (16/55)	0.581	27 (16/59)	22 (12/55)	0.511	22 (13/59)	22 (12/55)	0.978
Fatigue	53 (31/59)	25 (14/55)	0.003	46 (27/59)	20 (11/55)	0.004	41 (24/59)	13 (7/55)	0.001	31 (18/59)	7 (4/55)	0.002
Oral dryness	55 (32/58)	28 (15/53)	0.004	38 (22/58)	13 (7/53)	0.003	33 (19/58)	9 (5/53)	0.003	26 (15/58)	9 (5/53)	0.024
Ocular dryness	47 (27/58)	30 (16/53)	0.077	38 (22/58)	17 (9/53)	0.014	31 (18/58)	6 (3/53)	0.001	22 (13/58)	6 (3/53)	0.015
Skin dryness	48 (28/58)	46 (25/54)	0.834	38 (22/58)	31 (17/54)	0.474	29 (17/58)	26 (14/54)	0.689	22 (13/58)	17 (9/54)	0.444
Vaginal dryness	44 (22/50)	26 (13/50)	0.059	38 (19/50)	22 (11/50)	0.081	34 (17/50)	18 (9/50)	0.068	26 (13/50)	12 (6/50)	0.074
Week 24												
Global activity physician	72 (43/60)	61 (33/54)	0.233	58 (35/60)	51 (28/54)	0.487	48 (29/60)	41 (22/54)	0.416	38 (23/60)	33 (18/54)	0.579
Systemic activity physician	52 (31/60)	41 (22/54)	0.243	45 (27/60)	41 (22/54)	0.646	38 (23/60)	41 (22/54)	0.793	35 (21/60)	37 (20/54)	0.821
van Bijsterveld score	26 (10/38)	34 (12/35)	0.458	24 (9/38)	34 (12/35)	0.317	16 (6/38)	31 (11/35)	0.114	16 (6/38)	29 (10/35)	0.187
Schirmer's test	39 (22/56)	31 (14/45)	0.394	36 (20/56)	27 (12/45)	0.331	32 (18/56)	22 (10/45)	0.268	30 (17/56)	20 (9/45)	0.237
UWSF	44 (21/48)	20 (9/46)	0.012	44 (21/48)	20 (9/46)	0.012	38 (18/48)	17 (8/46)	0.029	35 (17/48)	15 (7/46)	0.025
ESR	73 (40/55)	31 (15/49)	<0.001	64 (35/55)	24 (12/49)	<0.001	55 (30/55)	16 (8/49)	<0.001	36 (20/55)	10 (5/49)	0.002
b_2 microglobulin	31 (15/49)	15 (7/47)	0.067	14 (7/49)	4 (2/47)	0.090	6 (3/49)	2 (1/47)	0.617	0	0	
Global activity patient	55 (33/60)	37 (20/54)	0.550	48 (29/60)	30 (16/54)	0.041	30 (18/60)	24 (13/54)	0.478	27 (16/60)	22 (12/54)	0.582
Pain	52 (31/60)	46 (25/54)	0.567	43 (26/60)	53 (23/54)	0.936	32 (19/60)	33 (18/54)	0.849	25 (15/60)	28 (15/54)	0.737
Fatigue	55 (33/60)	33 (18/54)	0.020	33 (20/60)	22 (12/54)	0.187	25 (15/60)	17 (9/54)	0.276	18 (11/60)	13 (7/54)	0.432
Oral dryness	52 (30/58)	25 (13/53)	0.003	40 (23/58)	13 (7/53)	0.002	29 (17/58)	9 (5/53)	0.009	16 (9/58)	8 (4/53)	0.192
Ocular dryness	48 (28/58)	33 (17/52)	0.097	36 (21/58)	19 (10/52)	0.048	29 (17/58)	13 (7/52)	0.045	24 (14/58)	10 (5/52)	0.044
Skin dryness	53 (30/57)	38 (20/52)	0.138	42 (24/57)	27 (14/52)	0.097	33 (19/57)	23 (12/52)	0.236	23 (13/57)	15 (8/52)	0.326
Vaginal dryness	47 (24/51)	36 (18/50)	0.260	45 (23/51)	28 (14/50)	0.075	39 (20/51)	28 (14/50)	0.233	33 (17/51)	26 (13/50)	0.420

The proportions of patients experiencing relative improvements (percentage of improvement vs baseline computed as the difference between baseline and post-treatment values divided by the baseline value) were compared between the rituximab and placebo groups. Improvements were increases for Schirmer's test and unstimulated whole salivary flow rate and decreases for all other variables. Global activity physician, systemic activity physician, global activity patient, pain, fatigue, oral dryness, ocular dryness, skin dryness and vaginal dryness were assessed using 100-mm VASs, where 0 indicated no symptom/activity and 100 mm the greatest possible symptom severity/activity. Four improvement cut-offs were chosen arbitrarily for all items, namely, 10%, 20%, 30%, and 40% vs baseline. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate. Bold type indicates statistically significant results ($P < 0.05$). PBO: placebo; RTX: rituximab; UWSF: unstimulated whole salivary flow; VAS: visual analogue scale.

Neither Schirmer's test nor the van Bijsterveld score were significantly better with rituximab compared with placebo. At week 24, UWSF response rates were significantly higher with rituximab using all cut-offs. The ESR improved significantly more often with rituximab at week 16 and to an even greater degree at week 24. The b_2 microglobulin levels were not significantly improved by rituximab.

To better explore the significance of ESR variation in our study, we assessed whether the decrease in ESR observed after rituximab in some patients was explained only by IgG decrease. We found a weak correlation

between ESR variation and IgG level variation after rituximab at week 24 (= 0.277). The median IgG decrease at week 24 was 1.7 g/l [interquartile range (IQR) 0.7- 3.5] in patients with a 530% ESR decrease vs 1.4 g/l (IQR 0.6- 2.1) in patients with a <30% ESR decrease at week 24 (P = 0.35). Three patient-reported and two objective outcome measures showed a 520% between-group difference at a given visit: VAS fatigue score, VAS oral dryness score, VAS ocular dryness score, UWSF and ESR.

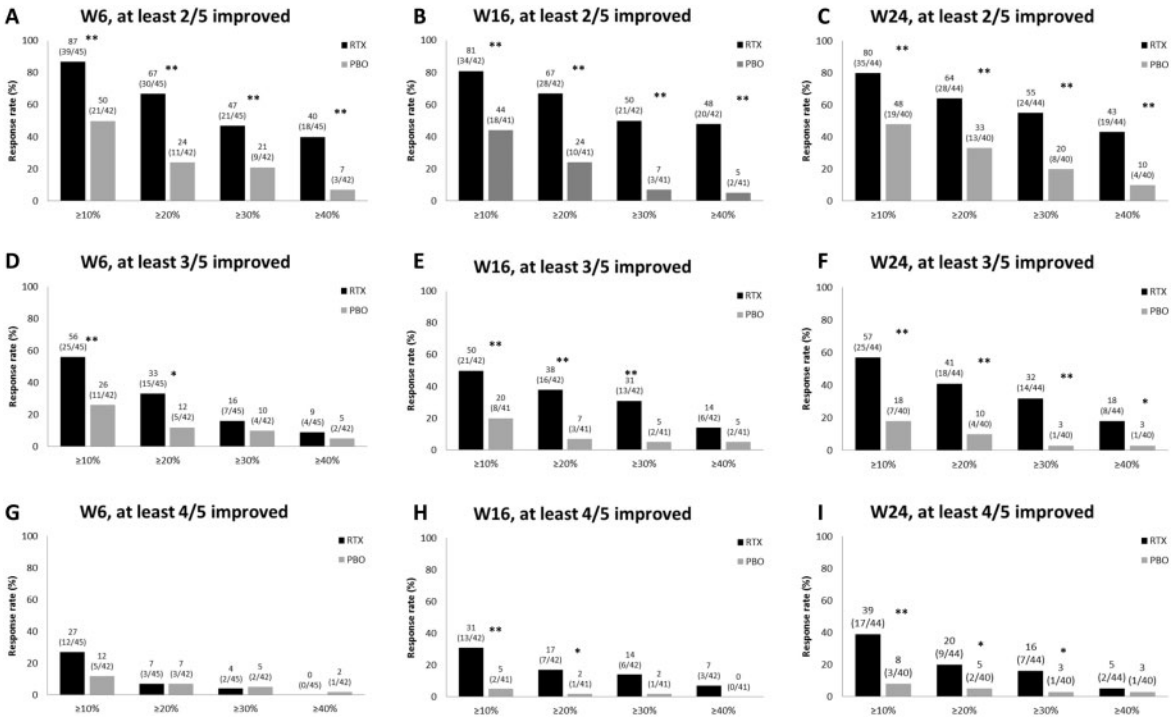
SSRI

We assessed the above-listed five outcome measures using different definitions of a response (Fig. 1). The response rate difference between the rituximab and placebo groups was largest when we defined a response as an improvement in at least two of the five outcome measures, along with a low response rate in the placebo group. We defined an SSRI-30 response a 530% relative improvement in at least two of these measures, since this definition displayed the largest between-group differences at weeks 16 and 24. At week 16, 50% of rituximab patients vs 7% of placebo patients had an SSRI-30 response (Fig. 1B). Corresponding proportions at week 24 were 55% vs 20% (Fig. 1C). If we considered more stringent criteria, such as 530% improvement in at least three of five outcome measures at week 24, the estimated placebo effect was much lower (3%) and the response rate in the rituximab group was 32%.

Markers for disease improvement in SSRI-30 responders

To assess the construct validity of the SSRI-30 response, we compared several variables between SSRI-30 responders and non-responders in the rituximab group (Table 2). A greater proportion of responders reported improved global health compared with baseline at weeks 16 and 24 and ascribed this improvement to the study medication. The SSRI-30 responder group had significantly larger improvements in mean VAS global activity and pain scores. The proportion of patients with

FIG. 1 Comparison of several composite endpoints based on the five outcome measures improved by rituximab in the TEARS trial



The five outcome measures are VAS fatigue score, VAS oral dryness score, VAS ocular dryness score, unstimulated whole saliva flow and ESR. (A- C) Response defined as an improvement in at least two of the five outcome measures. (D- F) Response defined as an improvement in at least three of the five outcome measures. (G- I) Response defined as an improvement in at least four of the five outcome measures. For each definition of response, we compared different levels of improvement vs baseline (10, 20, 30 and 40%) in single outcome measures at each time point. For example, in (A)- (C), the four groups of bars indicate the results obtained when defining a response as an at least 10, 20, 30 or 40% improvement vs baseline, from left to right. PBO: placebo; RTX: rituximab; TEARS: Tolerance and Efficacy of Rituximab in Sjögren's Disease; VAS: visual analogue scale; W: week. *P < 0.05, **P < 0.01 by chi-square test or Fisher's test as appropriate.

TABLE 2 Markers that improved in SSRI-30 responders to rituximab

	Week 16			Week 24		
	SSRI-30 responders (n = 21)	SSRI-30 non-responders (n = 21)	P-value	SSRI-30 responders (n = 24)	SSRI-30 non-responders (n = 20)	P-value
Global improvement, yes/no, % (n/N)	47.6 (10/21)	14.3 (3/21)	0.005	50.0 (12/24)	10 (2/20)	0.005
Treatment efficacy, yes/no, % (n/N)	71.4 (15/21)	45.0 (9/20)	0.086	66.7 (16/24)	30.0 (6/20)	0.015
VAS global activity score improvement, mean (S.D.)	19.1 (21.7)	1.5 (19.8)	0.007	25.4 (21.3)	0.5 (17.1)	<0.001
VAS pain score improvement, mean (S.D.)	13.9 (31.3)	2.6 (14.4)	0.048	17.3 (21.0)	8.4 (22.7)	0.001
ESSDAI improvement, mean (S.D.)	3.0 (5.2)	0.4 (5.5)	0.014	2.1 (3.6)	0.3 (5.4)	0.153
ESSDAI improvement 51, % (n/N)	81.0 (17/21)	38.1 (8/21)	0.005	62.5 (15/24)	30.0 (6/20)	0.032
SF-36 PCS improvement, mean (S.D.)	2.9 (6.3)	1.3 (5.3)	0.241	6.4 (7.0)	0.8 (5.7)	0.003
SF-36 MCS improvement, mean (S.D.)	4.9 (10.3)	3.1 (7.4)	0.696	2.7 (8.8)	0.3 (10.6)	0.917

Bold type indicates statistically significant results ($P < 0.05$). SSRI-30 response was defined as a 530% improvement vs baseline in at least two of five outcome measures among the VAS oral dryness score, VAS ocular dryness score, VAS fatigue score, unstimulated whole salivary flow and ESR. ESSDAI: EULAR SS Disease Activity Index; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short Form Health Survey; SSRI: SS Responder Index; VAS: visual analogue scale.

a 51 point ESSDAI improvement was higher among responders. Finally, the Physical Component Summary score of the 36-item short form quality of life scale was significantly improved in the SSRI-30 responders at week 24.

Changes in ESSDAI and ESSPRI in TEARS

We compared the rituximab and placebo groups regarding the proportions of patients with at least 10%, 20%, 30%, and 40% improvements in the ESSPRI and ESSDAI vs baseline at each time point (Fig. 2). The proportions of patients with a 520% ESSPRI improvement in the rituximab and placebo groups were 50% vs 25% at week 6, 44% vs 20% at week 16 and 45% vs 26% at week 24 ($P < 0.05$ for all comparisons) (Fig. 2A–C). Corresponding proportions for the ESSDAI were not different between the rituximab and placebo groups at any of the time points (Fig. 2D–F).

External validation of the SSRI-30

In the only other published randomized controlled trial of rituximab in pSS, the single-centre study by Meijer et al. [9], the SSRI-30 responder rates in the rituximab and placebo groups were respectively 68% (13/19) vs 40% (4/10) at week 12 and 74% (14/19) vs 40% (4/10) at week 24 (Fig. 3A). Thus the SSRI-30 was able to detect a therapeutic effect of rituximab in this trial.

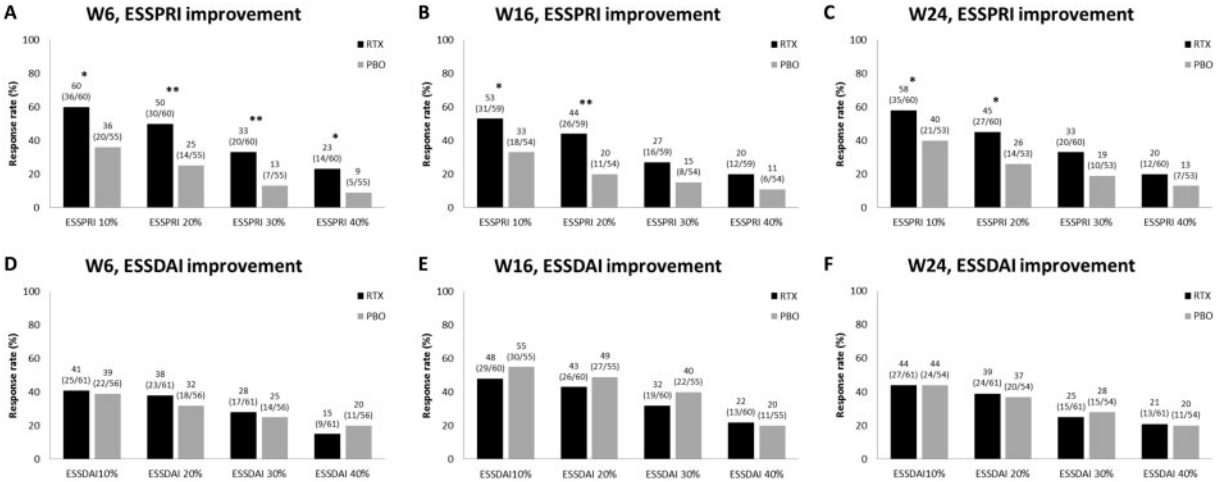
Conversely, the SSRI-30 response rates were not significantly different between the infliximab and placebo groups in the TRIPSS trial [40.4% (19/47) vs 34.9% (15/43) at week 10 and 40.9% (18/44) vs 37.5% (15/40) at week 22; Fig. 3B], confirming the lack of efficacy of infliximab in pSS.

Discussion

Our post hoc analysis of TEARS study data identified five outcome measures that were significantly improved by rituximab compared with a placebo in patients with pSS. Combining these five outcome measures produced a composite index, the SSRI. We defined an SSRI-30 response as a 530% improvement in at least two of the five outcome measures. The SSRI-30 detected a larger response rate with rituximab vs placebo in another randomized controlled trial, but showed no significant difference between treatment groups in a randomized controlled trial of infliximab. These results are in accordance with the clinical observation that infliximab was not but rituximab was effective in pSS patients, and support the external validity of the SSRI-30. Similar to criteria sets used in other autoimmune diseases, the SSRI includes both patient-reported measures and objective measures. Although the SSRI comprises no objective measures of extraglandular signs, these signs improved in SSRI-30 responders. Therefore the SSRI-30 might prove useful for assessing treatment efficacy in future trials in pSS.

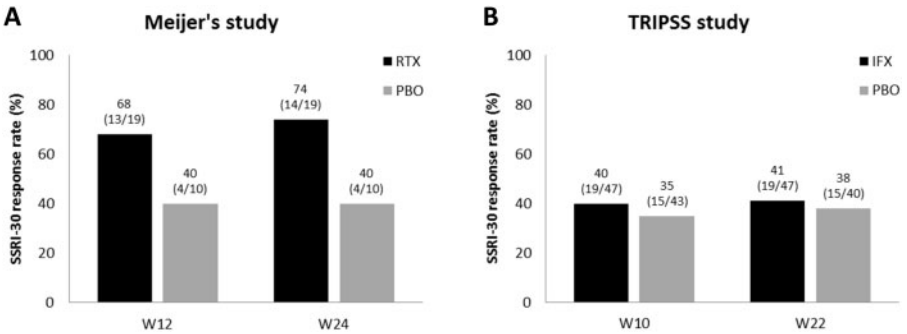
This work is based on the assumptions of a positive effect of rituximab in pSS, as suggested by clinical observations and open-label studies, and of an inability of the primary endpoint of the TEARS trial to detect this effect. Indeed, in the absence of validated response criteria, the choice of a primary endpoint when designing a study is inevitably a bet mainly based on expert opinion. At this stage of clinical research in the field of pSS therapy, studies like the present one are needed in order to provide evidence to choose the best evaluation criteria in the design of future studies. The objective of this study was not to prove the efficacy of rituximab in pSS, but to develop a new tool for future trials.

FIG. 2 Changes in the ESSPRI and ESSDAI as endpoints



Response rates in the rituximab and placebo groups were compared using the chi-square test or Fisher's test as appropriate. Improvement cut-offs used to define a response were 10, 20, 30 and 40% vs baseline. For instance, ESSPRI/ESSDAI 10% indicates that a response was defined as a 510% decrease in the ESSPRI or ESSDAI vs baseline. ESSDAI: EULAR SS Disease Activity Index; ESSPRI: EULAR Sjgren's Syndrome Patient-Reported Index; PBO: placebo; RTX: rituximab; W: week. *P < 0.05, **P < 0.01.

FIG. 3 Application of the SSRI-30 in other trials



SSRI-30 response rates (defined as the proportion of patients experiencing a 530% relative improvement in at least two measures among VAS fatigue score, VAS oral dryness score, VAS ocular dryness score, unstimulated whole salivary flow and ESR) were assessed in the Meijer et al. rituximab placebo-controlled trial [9] and in the TRIPSS infliximab placebo-controlled trial [17]. IFX: infliximab; PBO: placebo; RTX: rituximab; VAS: visual analogue scale; W: week.

As illustrated in Fig. 1, several definitions of a response can be computed based on the five selected items. The most sensitive definitions (improvement of at least one or two items, and/or improvement of at least 10% or 20% from baseline) led to high response rates in the rituximab group, but also to a high placebo effect. Conversely, the most stringent definitions of response decreased the placebo effect, but also the response rate in the active arm. Therefore we considered that the SSRI-30 definition was the best compromise, with the largest response rate difference between the two groups and a low placebo effect.

Validated outcome measures suitable for use as endpoints in clinical trials of pSS are challenging to develop, for several reasons. First, active disease is difficult to define, as the main symptoms in many patients are subjective complaints of fatigue and dryness. This fact prompted the EULAR to develop a patient-reported index of disease activity, the ESSPRI, which is based on the patient's perceptions [14]. In contrast, the ESSDAI tool for assessing systemic disease relies on physician assessments of physical and laboratory signs [13]. Neither the ESSPRI nor the ESSDAI has yet been used as the primary endpoint in prospective randomized therapeutic trials. Second, pSS usually has a slow pace of progression, with no clearly defined flares. Gradual worsening of the symptoms over several months or years raises

challenges in detecting improvements during short-term studies. Furthermore, no simple criteria for evaluating long-term disease progression are available for use as the reference standard against which new tools can be assessed [18]. Third, and most importantly, no specific treatments have been proven to affect the course of pSS. Consequently, the sensitivity to change of outcome measures is difficult to assess. Thus, in the ESSPRI and ESSDAI validation studies, the vast majority of patients had the same level of disease activity at both time points [15].

The TEARS study, a large randomized placebo-controlled double-blind therapeutic trial, provides a unique opportunity to identify outcome measures that are sensitive to change and that might therefore be useful endpoints for clinical trials. Whether patient-reported dryness and other subjective symptoms reflect disease activity or the extent of permanent exocrine gland damage is debated [19]. An unexpected finding from the TEARS study was that subjective fatigue, oral dryness and ocular dryness were improved by rituximab, whereas other patient-reported outcomes such as limb pain and global activity were unchanged. Among objective measures, the UWSF has limitations, including marked variability [20], which decreases gradually over a relatively short period of a few years [21], and may therefore be useful for assessing treatment effects in patients with early pSS. The TEARS study documented a significant UWSF increase with rituximab therapy over a period of only 24 weeks. In a prospective study of patients with early active pSS, UWSF showed a larger increase over a longer period, of 120 weeks, with two rituximab infusions every 24 weeks [7]. Conversely, other objective measurements of ocular dryness, such as Schirmer's test and ocular dye staining, seemed insensitive to change. Salivary gland ultrasonography might prove useful to evaluate the response to therapy in pSS [22], but has not been routinely used up to now. The last component of the SSRI, the ESR, mirrors the biological activity of CTDs, as it reflects the levels of hypergammaglobulinaemia, circulating immune complexes, RFs and other mediators of inflammation [23, 24]. Hypergammaglobulinaemia and high IgG levels are well accepted activity markers in pSS and are included in the ESSDAI. However, in a trial assessing rituximab efficacy, we considered that a decrease in IgG levels could be explained either by the mechanism of action of the drug or by an improvement in disease activity. ESR has been used once in a trial to assess the response to a treatment in pSS [25]. ESR is a marker of both inflammation and hypergammaglobulinaemia and is included in the various response criteria for RA (even in rituximab studies). We found that the correlation between ESR and IgG variations after rituximab was weak in the TEARS study. Thus the ESR decrease after rituximab may reflect an improvement in autoimmunity-induced inflammation in pSS patients.

That the ESSDAI was unchanged by rituximab therapy in the TEARS study is probably ascribable to the small proportion of patients with clinically relevant systemic manifestations requiring immunosuppressive therapy. Severe systemic complications are rare in pSS: although the ESSDAI is 51 in >90% of patients at some point during the course of their disease [26], <15% of pSS patients have clinically relevant extraglandular involvement [27]. The mean baseline ESSDAI in our patients was 10 and the decrease was similar in the rituximab and placebo groups. Conversely, in Meijer et al.'s rituximab study [9] that included patients with a shorter disease duration, more frequent systemic involvement and biological activity, the ESSDAI was reliable and detected treatment effects until up to week 24 [28]. The ESSDAI may therefore be useful in the minority of pSS patients with systemic involvement. Our analysis could be limited by the retrospective computation of the ESSDAI, which had not yet been published at the time of study initiation, so some ESSDAI items were not included in the patients' records.

This work has several limitations. The post hoc design of the study, which aimed to select a posteriori the items that best discriminated between patients who received rituximab or placebo, may artificially increase the response rates in the rituximab group while decreasing the measured placebo effect. However, the fact that noticeable differences in response rates were also found in Meijer et al.'s study [9] strengthens our findings, even if the number of participants in this latter study was small. We have limited evidence, based on these available data, to assess whether SSRI response represents real and important improvement in disease activity and patients' health-related quality of life. Future prospective studies focusing on the definition of what is considered important improvement by patients are needed.

Our study constitutes a step toward the development of reliable and validated outcome measures suitable for use in future therapeutic trials in pSS. However, its results remain preliminary. Further external validation of the SSRI will be possible when the TRACTISS trial is published [10]. Whether the SSRI is suited only to assessments of rituximab or also to those of other drugs remains unknown. However, trials are currently under way to assess other drugs [e.g. abatacept in the ASAPIII study (NCT02067910) and tocilizumab in the ETAP trial (NCT01782235)]. Once several large trials assessing various drugs in pSS are completed, a joint analysis will be possible that will provide additional material for developing generalizable outcome measures, similar to the development of ACR response criteria for RA 20 years ago [29, 30].

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Supplementary data

Supplementary data are available at Rheumatology Online.

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