Effects of rituximab therapy on quality of life in patients with primary Sjögren's syndrome

V. Devauchelle-Pensec[1,3], J. Morvan[1], A.C. Rat[6], S. Jousse-Joulin[1,3], Y. Pennec[2], J.O. Pers[3], C. Jamin[3], Y. Renaudineau[3], I. Quintin Roue[4], B. Cochener[5], P. Youinou[3], A. Saraux[1,3]

[1]Rheumatology Unit and [2]Internal Medicine Unit, la Cavale Blanche Teaching Hospital, Brest, France; [3]Immunology Laboratory, [4]Pathology Unit and [5]Ophthalmology Unit, Morvan Teaching Hospital, Brest, France; [6]Rheumatology Unit and EA 4003, Inserm CIC-EC, Brabois Teaching Hospital, Nancy, France.

Abstract

Objectives

To assess the efficacy of the anti-CD20 antibody rituximab in improving physical function and health-related quality of life (HRQoL) in patients with active primary Sjögren's syndrome (pSS), as well as the duration and sources of HRQoL improvements.

Methods

Sixteen patients with pSS received rituximab infusions (375 mg/m^2) at weeks 0 and 1 and were followed up for 36 weeks. All patients fulfilled 2002 American-European Consensus Group criteria for pSS and had active disease defined as scores >50 mm on two of four 100-mm visual analogue scales (VAS) evaluating global disease activity, fatigue, pain, and dryness. Standardised evaluations including the Short Form 36 Health Survey (SF-36) were conducted. SF-36 score changes from baseline to weeks 12, 24, and 36 were assessed.

Results

Baseline mean SF-36 scores were considerably decreased, compared to the general same-age population. Role-physical (14.1±27.4), role-emotional (12.5±29.9), vitality (26.2±14.3), and general health (32.6±11.2) were the dimensions with the worst scores. Twelve weeks after rituximab, the mental component summary score was improved in 15 patients (mean improvement, 31.2±36.4, p=0.001) and the physical component summary score in 14 patients (mean improvement, 16.9±26.2, p=0.049). Further improvements occurred from week 12 to week 24, and most of the gains were sustained at week 36.

Improvements in the physical and mental component summary scores failed to correlate with improvements in the VAS scores.

Conclusion

Substantial alterations in HRQoL were noted in patients with pSS. Rituximab infusions without corticosteroid therapy produced meaningful improvements in HRQoL. Controlled studies of rituximab are needed.

Key words

primary Sjögren's syndrome, rituximab, health-related quality of life, SF-36

Valérie Devauchelle-Pensec, MD, PhD
Johanne Morvan, MD,
Anne-Christine Rat, MD, PhD
Sandrine Jousse-Joulin, MD
Yves Pennec, MD
Jacques Olivier Pers, DDS, PhD
Christophe Jamin, PhD
Yves Renaudineau, PharmD, PhD
Isabelle Quintin Roue, MD
Beatrice Cochener, MD, PhD
Pierre Youinou, MD, DSc
Alain Saraux, MD, PhD

This study received financial support from the Brest Teaching Hospitals and the 2003 Hospital Clinical Research Program (PHRC 2003).

Please address correspondence and reprint requests to:
Prof. A. Saraux,
Service de Rhumatologie,
Hôpital Universitaire de la Cavale Blanche,
BP 824, F 29609 Brest Cedex, France.
E-mail: alain.saraux@chu-brest.fr

Received on March 21, 2010; accepted in revised form on June 25, 2010.

Competing interests: none declared.

Introduction

Primary Sjögren's syndrome (SS) is an autoimmune disorder with a prevalence of 0.2% to 3% in the general population (1). Chronic inflammation and fibrosis of the salivary and lachrymal glands constitute the hallmark of pSS. The main clinical symptoms are xerostomia, xerophthalmia, arthralgia, and severe fatigue. Nevertheless, pSS is a systemic disorder that can cause a wide variety of clinical manifestations and laboratory test abnormalities where hematologic complications can induce lymphoma and increase mortality. The multiplicity of the symptoms, importance of subjective symptoms, and frequently delayed diagnosis may have an adverse effect on mental health. Severe alterations may develop in functional abilities and social participation, as well as in general health perception, energy, and health-related quality of life (HRQoL) (2). The development of better criteria for disease activity (3, 4) and the introduction of new treatments are generating hope that patient self-perception will improve in the near future.

Several questionnaires are available for assessing fatigue and general health in patients with pSS or other rheumatic diseases, such as the Hospital Anxiety and Depression Scale (HAD) (5), the brief version of the World Health Organization's multicultural quality-of-life instrument (WHOQOL-BREF) (6), the Symptom Checklist-90-R (SCL-90-R) (7), and the 36-item Short Form health survey (SF-36) (8). The SF-36 is a generic quality-of-life questionnaire that has been validated in patients with systemic lupus erythematosus, rheumatoid arthritis (RA), and pSS, three conditions in which it demonstrated marked alterations in HRQoL (9-12).

Rituximab (Rituxan®/MabThera®; Roche Pharmaceuticals, UK) is a chimeric monoclonal antibody against CD20 that was initially developed for B-cell lymphoma and subsequently used in chronic idiopathic thrombocytopenic purpura, autoimmune haemolytic anemia, myasthenia gravis, and Wegener's granulomatosis (13). Controlled studies established that rituximab produced marked and sustained improvements in patients with RA (14). Two open-label studies suggested a therapeutic effect in patients with pSS, which is considered to be a B-cell driven disease (15, 16) and one controlled study in a few number of patients confirmed this efficacy (16). In our previous study (17), benefits were apparent at week 12 and persisted until the last evaluation at week 36. To avoid bias, this study was conducted without concomitant corticosteroid treatment.

Treatment goals in patients with pSS include not only evaluation of extraglandular symptoms (fatigue, pain, synovitis, neurological manifestations, pulmonary disease, and purpura) and glandular symptoms (salivary gland hypertrophy and dryness), but also improvements in HRQoL. The objectives of this study were to assess the potential effects of rituximab therapy without corticosteroid therapy on physical function and HRQoL in patients with active pSS, to determine the duration of HRQoL improvements, and to gain insight into the factors that may contribute to the HRQoL gains.

Materials and methods

Study population

As previously described (17), sixteen patients were enrolled in two departments (Rheumatology and Internal Medicine) at the University Hospital in Brest (France) between April and December 2004. Patients were eligible if they fulfilled 2002 American-European Consensus Group criteria for pSS (18) and had active disease defined as scores greater than 50 mm on at least two of four 100-mm visual analogue scales (VAS) for global disease activity (including extraglandular manifestations), pain, fatigue, and dryness, respectively, over the last week. Additional inclusion criteria were as follows: age 18-50 years, stable regimen of non-steroidal anti-inflammatory drug therapy, and no prescription of immunosuppressive agents within the last 4 weeks. Patients were not included if they had secondary SS; received cytotoxic drugs within the last 4 months; had a history of severe renal or haematological failure, cancer, hepatitis B or C, HIV, tuberculosis, severe diabetes, or any other chronic disease or evidence of infection; or if they

were unable to understand the protocol. The study design was approved by our institutional review board and by the Brest ethics committee. All patients gave their written informed consent.

Treatment protocol

All 16 patients received 375 mg/m^2 of intravenous rituximab at weeks 0 and 1. The infusion rate was 50 mg/hour initially and was increased every 30 minutes to a maximum of 400 mg/hour if the drug was well tolerated. Symptoms of hypersensitivity or infusion-related reactions were sought every 30 minutes. Stable symptomatic treatment of oral and ocular discomfort was provided during the follow-up. This protocol was modified after the first 2 subjects had experienced side-effects due to the infusion rate of 200 mg/hour. Then, the patients received increasing rate of rituximab infusions, up to a maximum rate of 100 mg/hour. No corticosteroids or immunosuppressive drugs were given.

Patient-reported outcome measures

Patients completed the validated French version of the SF-36 (19, 20) at baseline (before the first rituximab infusion) and at weeks 12, 24, and 36. The 36 items of the SF-36 explore eight dimensions: physical functioning, role limitation due to physical health (role-physical), bodily pain, general health, vitality, social functioning, role limitation due to emotional factors (role-emotional), and mental health. A standardised score from 0 (worst QoL) to 100 (best QoL) is obtained for each dimension. Two summary scores can be computed, one for the physical component of the survey and the other for the mental component. We used the US scoring algorithms, which have been found equivalent to French algorithms (21). Three dimensions (physical functioning, role-physical, and bodily pain) contribute most of the physical component summary score (PCSS) and three components (mental health, role-emotional, and social functioning) most of the mental component summary score (MCSS). The two remaining dimensions, vitality and general health, show moderate correlations with both the PCSS and the MCSS. The two summary scores have a mean of 50 and a standard deviation of 10 in the general population in the US.

The two summary scores have a mean of 50 and a standard deviation of 10 in the general population in the US.

The patients completed VASs for dryness, pain, disease activity, and fatigue at baseline and at weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

Clinical evaluations

All patients underwent standardised evaluations including a physical examination and routine laboratory tests at baseline and at weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36. All patients underwent a physical examination of the 18 fibromyalgia tender points and swollen joint counts (interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, hip, knee, ankle, and metatarsophalangeal joints; n=42), that were recorded at weeks 0, 12, 24, and 36. Extra glandular manifestations were noted. Xerostomia and xerophthalmia were evaluated at weeks 0, 12, and 36; xerostomia was assessed using the unstimulated salivary flow rate (5 minutes; samples were weighed, and 1 mg was taken to correspond to 1 ml) and xerophthalmia was evaluated by an ophthalmologist (BC) using the Schirmer test and the van Bijsterveld score (22, 23). The Chisholm score (24) was determined on labial accessory salivary gland biopsy samples at inclusion and at week 12.

The following laboratory tests were performed at each visit: erythrocyte sedimentation rate, serum C-reactive protein, and blood cell counts; renal and liver function tests; serum creatine phosphokinase; serum IgG, IgA, and IgM by nephelometry; and quantification of serum gammaglobulins by serum protein electrophoresis. Immunological tests were obtained at weeks 0, 12, and 36; they consisted of latex tests and isotype-specific in-house ELISAs for IgM, IgG, and IgA rheumatoid factor; tests for anti-citrullinated antibodies; antinuclear antibody determination using an in-house indirect immunofluorescence test with HEp-2 cells as the substrate; and tests for IgA-, IgG-, and IgM-containing immune complexes. B- and T-cell subpopulations were evaluated using an Epics-XL flow cytometer (Beckman-Coulter, Hialeh, FL) with EDTA-treated blood.

Statistical analysis

Version 12.0 of the Statistical Package for the Social Sciences software for Windows (SPSS, Chicago, IL) was used. Data are reported as means±SD. Data at baseline were compared to data at weeks 12, 24, and 36 using the Wilcoxon matched-pairs signed-rank test for paired data. *P*-values of less than 0.05 were considered significant. For each of the eight SF-36 dimensions, we determined whether the change constituted at least a minimal clinically important difference, defined as a 5-point difference between values at two time points. Given the small sample size and the non-normal distribution of some of the SF-36 scores (25, 26), we computed the medians in addition to means and standard deviations. Spearman's rank correlation coefficient was used to assess correlations between SF-36 scores and VAS scores.

Results

Patient characteristics

We included 16 patients (14 females and 2 males) with a mean age of 54.9±12.9 years and a mean disease duration of 13.3±10.3 years. Antinuclear antibodies were detected in all 16 patients, anti-SSA in 13 patients, and anti-SSB in 7 patients. The baseline VAS pain score was high in all 16 patients. Table I lists the main patient characteristics.

By physical examination, 9/16 (56%) had pain to palpation of fibromyalgia tender points, among whom only two had more than 11 tender points. Concerning extra glandular manifestations, one patient was treated for long time for hypothyroidism and two had a long history of depressive syndrome. One had past history of myositis and two had past facial palsy. Active manifestations were for one patient bronchitis, one had active tubulopathy and one had minor manifestation of cutaneous vasculitis. None had parotid gland enlargement or fever. After rituximab tretament, as previously described (17), bronchitis and vascularitis resolved, and the IgA-RF titers were significantly decreased at week 36). IgM level decreased at

Table I. Patient characteristics at baseline.

Patient characteristics	mean±SD
Global disease activity VAS, mm	71.9 ± 13.4
Pain VAS, mm	60.4 ± 19.2
Fatigue VAS, mm	77.3 ± 14.5
Dryness VAS, mm	8.4 ± 11.9
Tender point count	4.5 ± 6
Tender joint count	6 ± 10.9
Swollen joint count	1 ± 0.9
Salivary flow rate ml/min	0.1 ± 0.1
Schirmer test, mm	8.4 ± 8.3
Focus score (mean±SD)	1.6 ± 1.7
Chisholm score ≥3 Number of patients	9/15
ESR, mm/hour	30.1 ± 26
IgA-RF, IU	0.3 ± 0.3
Latex test	14.8 ± 21.7
Presence of Anti-SSA	13/16
Presence of Anti-SSB	9/16
IgA, mg/liter	2.7 ± 1.2
IgG, mg/liter	20.1 ± 13.2
IgM, mg/liter	1.41 ± 0.57

VAS: visual analogue scale; ESR: erythrocyte sedimentation rate, RF: rheumatoid factor; IU: international unit; Ig: immunoglobuline; Anti-SSA: anti-SSA antibodies.

week 12 (p<0.01) but was normal at week 36.

Quality of life at baseline

Baseline scores for all eight SF-36 dimensions were available for the 16 patients. As expected, a non-normal distribution was noted for some of the dimensions. The mean PCSS was 34.5±7.4 and the mean MCSS was 31.6±8.1. Thus, both values were markedly lower than 50, the mean in the general population, indicating severe impairments in quality of life. In addition, the mean scores on the eight SF-36 dimensions were lower than the mean scores reported in a population-based survey conducted in France in women aged 45-64 years (Institut National de la Statistique et des Études Économiques (27) (Table II). Physical health and mental health were affected in equal measure. The four most severely affected dimensions were role-physical (14.1±27.3), role-emotional (12.5±24), vitality (26.2±14.3), and general health (32.6±11.2).

At baseline, the PCSS showed no significant correlations with any of the VAS scores, and the MCSS correlated only with the bodily pain score (Table III).

Quality of life improved 12 weeks after rituximab therapy

At week 12 after the first rituximab infusion, the MCSS was improved in 15 patients and the PCSS in 14 patients. Mean improvements were 31.2±36.4 (p=0.001) on the MCSS and 16.9±26.2 (p=0.049) on the PCSS. The improvement at week 12 was 25% or greater in 9 patients for the MCSS and 5 patients for the PCSS (data not shown). All eight SF-36 dimensions were improved to a degree that far exceeded the minimal clinically important difference (Fig. 1).

Quality-of-life improvements were sustained 36 weeks after rituximab therapy

Changes in SF-36 scores from baseline to week 36 are shown in Figure 1. Improvements were greatest at week 24 but remained substantial statistically significant at week 36. We also looked for the correlation between improvements in PCSS and MCSS values from baseline to week 36. Although the two summary scores correlated well with each other in a few patients, we found no statistically significant association between PCSS and MCSS improvements at any of the time points, including week 24 (r= -0.335; p=0.204) (data not shown).

Improvements in the PCSS, MCSS, and VAS scores showed similar changes over time (Fig. 2). At week 24, the PCSS improvement correlated strongly with the improvements in VAS scores for dryness, pain and fatigue, whereas the improvement in MCSS failed to correlate significantly with any of the VAS scores (Table IV), although seven patients of 16 at week 24, 7 of 15 at week 32 and 9 of 15 at week 36 improved their 4 VAS scores: global, pain, fatigue, and dryness.

Discussion

We conducted an open-label study to assess the potential efficacy of rituximab in improving quality of life in patients with pSS. That quality of life is severely altered in patients with pSS has been established using the SF-20, SF-36 questionnaire, and the WHOQOL-BREF. These components, were not strictly validated for pSS and probably should be adapted, however, they are commonly used by authors. After the recent elaboration of an activity score, the Eular committee should developpe specific questionnaire for Sjögren quality of life (28). In keeping with these data, we found markedly decreased scores on all eight SF-36 dimensions in

Table II. SF-36 scores at weeks 0, 12, 24 and 36; rituximab was given at weeks 0 and 1.

	INSEE*	Baseline (n=16)		Week 12 (n=16)		Week 24 (n=13)		Week 36 (n=14)	
	(n=20574)	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Physical functioning	85.3 ± 22.3	50.9 ± 30.2	60	65.9 ± 19.4	72.5	64.3 ± 24.2	75	62.8 ± 23.1	65
Role-physical	82.2 ± 32.2	14.1 ± 27.3	0	40.6 ± 40.7	50	48.3 ± 39.5**	50	35 ± 39.9	25
Bodily pain	73.0 ± 24.6	41.4 ± 14.5	41	54.2 ± 20.6**	51	54.2 ± 22.1	51	55.6 ± 26.1	51
Mental health	66.7 ± 17.7	45.5 ± 16.2	44	54 .2 ± 15**	52	53.3 ± 14.5**	52	53.9 ± 14.9	52
Role-emotional	82.0 ± 32.9	12.5 ± 24	0	60.4 ± 38.9***	66.6	57.8 ± 42.7***	66.7	33.3 ± 41.8	0
Social functioning	80.9 ± 21.2	41.4 ± 14.9	37.5	53.9 ± 25.3**	62.5	55 ± 25.4**	50	56.7 ± 20.5*	50
Vitality	57.4 ± 18.0	26.2 ± 14.3	25	44.1 ± 19.3***	42.5	43 ± 22.9***	40	37 ± 24.6	30
General health	67.8 ± 18.9	32.6 ± 11.2	35	41.9 ± 16.4**	38.5	42.9 ± 18.7**	42	42.8 ± 23.6	35

*INSEE: Institut National de la Statistique et des Études Économiques. Age 45–64 years, 53% of women (27). **p<0.05; ***p<0.001.

Table III. Correlations linking the physical and mental component summary scores of the SF-36 and the visual analogue scale scores for global disease activity, pain, fatigue, and dryness.

		VAS disease activity	VAS pain	VAS fatigue	VAS dryness
PCSS	*r*	-0.06	-0.06	-0.08	-0.10
	p	0.83	0.83	0.77	0.74
MCSS	*r*	-0.40	-0.27	-0.63	-0.26
	p	0.13	0.31	0.009*	0.37

r: Spearman's correlation coefficient; *p*: statistical significance level; PCCS: Physical Component Summary Score on the SF36; MCSS: Mental Component Summary Score on the SF36; VAS: visual analogue scale.

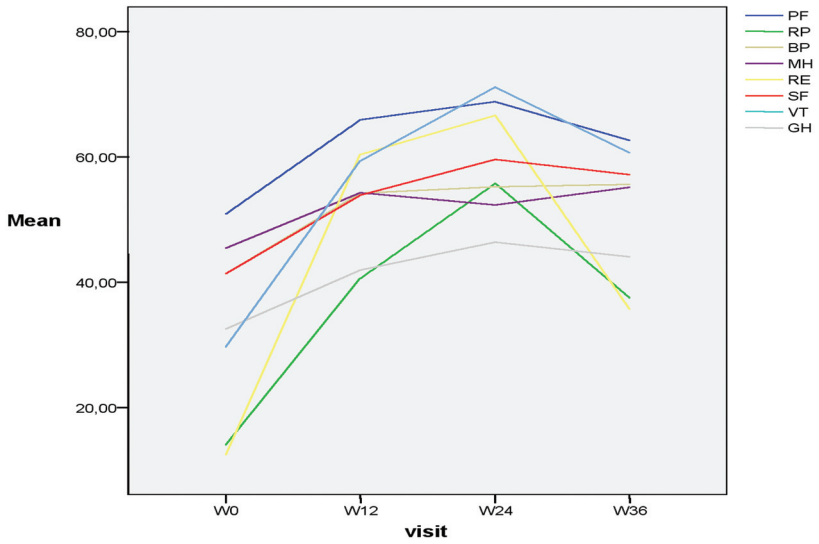

Fig. 1. Scores on each of the eight dimensions of the SF-36 questionnaire at baseline and at weeks 12, 24, and 36 after the first of two rituximab infusions given 1 week apart.
PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health.

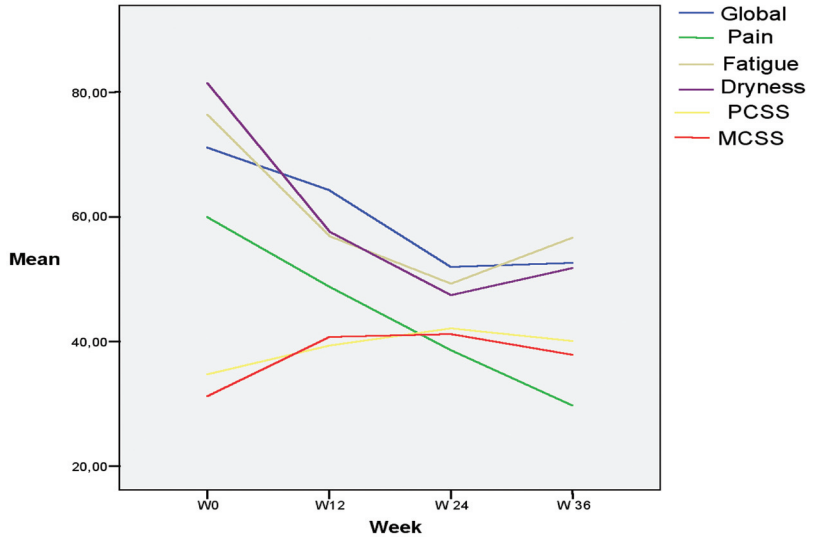

Fig. 2. Mean values of the mental and physical component summary scores of the SF-36 and of the four visual analogue scale scores (pain, fatigue, dryness, and global disease activity), at baseline and at weeks 12, 24, and 36.
PCSS: Physical Component Summary Score on the SF36; MCSS: Mental Component Summary Score on the SF36. For both summary scores, 0 indicates the worst possible quality of life and 100 the best possible quality of life. The four visual analogue scales were 100-mm scales where 0 indicated absence of the symptom (or inactive disease) and 100 the greatest severity possible.

our patients with pSS compared to the general population and women 45-64 years of age living in France.

Moreover some symptoms such as fatigue and chronic pain in the muscles and tendons are common features in pSS. The mechanisms that underlie muscle and tendon pain in pSS are unknown. However, a prevalent hypothesis is that fibromyalgia is a common concomitant of pSS (3-6) increasing marked disability and quality-of-life alterations. In our population, although 56% of patients had clinical tender points only two patients were diagnosed as fibromyalgia in accordance to ACR criteria. This could not explain at inclusion the poor quality of life. Other clinical condition such as thyroid abnormalities could induce poor quality of life but only one patient had been treated in the past for hypothyroidism.

Quality of life was poorer in our population than in several large studies of patients with pSS. This difference can be ascribed to our inclusion criteria, which selected patients who had scores greater than 50 mm on at least two of four 100-mm VASs for global disease activity, fatigue, pain, and dryness. Consistent with earlier studies, the three most severely affected dimensions were role-physical, role-emotional, and vitality. Surprisingly, except for physical functioning, scores were lower in our study of pSS than in earlier studies of RA (29, 30).

Twelve weeks after rituximab therapy without concomitant corticosteroid administration, six SF-36 dimensions were significantly improved, namely, bodily pain, mental health, role-emotional, social functioning, general health, and vitality. In all six dimensions, the criterion for a minimal clinically significant difference was achieved. Improvements were largest in the role-emotional and vitality dimensions, where the changes exceeded 15 points, indicating clinically important differences. Disabling fatigue is a major problem for many patients with pSS (31, 32) and may hold promise as a criterion for evaluating disease activity or treatment efficacy. Dass *et al*. (33) also described improvement in fatigue when patients with pSS were treated with rituximab.

Table IV. Correlation between improvements in the physical and mental component summary scores of the SF36 and the improvements in the visual analogue scores for global disease activity, pain, fatigue, and dryness, at week 24.

		VAS disease activity	VAS pain	VAS fatigue	VAS dryness
PCSS improvement	*r*	0.467	0.808	0.625	0.694
	p	0.108	0.001	0.022	0.012
MCSS improvement	*r*	0.324	0.192	.485	0.277
	p	0.28	0.529	0.093	0.384

r: Spearman's correlation coefficient; *p*: statistical significance level; PCCS: Physical Component Summary Score on the SF36; MCSS: Mental Component Summary Score on the SF36; VAS: visual analogue scale.

The perceptions explored by the vitality dimension of the SF-36 show only partial overlap with those explored by the VAS for fatigue. In our patients, the VAS fatigue score decreased significantly after rituximab therapy. These improvements are consistent with those shown by the vitality score and suggest that the VAS fatigue scale may deserve an important place among criteria used to assess treatment efficacy.

Surprisingly, the PCSS and MCSS values failed to correlate with three of the four VAS scores, the exception being fatigue. During follow-up, PCSS improvements correlated significantly with improvements in VAS scores for pain, fatigue, and dryness but not with improvements in the VAS score for global disease activity. This result indicates that quality-of-life alterations in pSS are due to multiple factors, with fatigue playing a prominent role. Several instruments are required to assess HR-QoL in patients with pSS, among which the VAS for fatigue may be suitable for use in clinical practice or therapeutic trials.

SF-36 improvements were greatest at week 24. At this time point, the PCSS improvement correlated closely with VAS scores for dryness, pain, and fatigue. In contrast, MCSS improvements failed to correlate significantly with any of the VAS scores, although a moderate correlation was noted with the VAS fatigue score (r=0.48). Interestingly, the MCSS improved clearly after rituximab therapy, suggesting a mental health improvement that was unrelated to the symptoms measured by the VAS scores. In addition, the MCSS improvement was not correlated with the PCSS improvement, further supporting a role for unidentified factors in the mental health gains. However, a randomised controlled trial is needed to establish that the significant gains in the role-emotional, social functioning, and mental health dimensions were not due, at least in part, to a placebo effect.

Our findings suggest that rituximab may hold promise for improving HR-QoL in patients with pSS patients. After two rituximab infusions, improvements were greatest at week 24 and sustained at week 36. Randomised controlled trials are needed to rule out bias due to a placebo effect.

References

1. THOMAS E, HAY EM, HAJEER A, SILMAN AJ: Sjögren's syndrome: a community-based study of prevalence and impact. *Br J Rheumatol* 1998; 37: 1069-76.
2. CHAMPEY J, CORRUBLE E, GOTTENBERG JE *et al*.: Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. *Arthritis Rheum* 2006; 55: 451-7.
3. BOWMAN SJ, BOOTH DA, PLATTS RG: Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. *Rheumatology* (Oxford) 2004; 43: 758-64.
4. VITALI C, PALOMBI G, BALDINI C *et al*.: Sjögren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum* 2007; 56: 2223-31.
5. ZIGMOND AS, SNAITH RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
6. Development of the World Health Organization WHOQOL-BREF quality of life assessment. THE WHOQOL GROUP. *Psychol Med* 1998; 28: 551-8.
7. DEROGATIS LR: Misuse of the symptom checklist 90. *Arch Gen Psychiatry* 1983; 40: 1152-3.
8. WARE JE, KOSINSKI M: Interpreting SF-36 summary health measures: a response. *Qual Life Res* 2001; 10: 405-13; discussion 415-20.
9. LWIN CT, BISHAY M, PLATTS RG, BOOTH DA, BOWMAN SJ: The assessment of fatigue in primary Sjögren's syndrome. *Scand J Rheumatol* 2003; 32: 33-7.
10. SUTCLIFFE N, STOLL T, PYKE S, ISENBERG DA: Functional disability and end organ damage in patients with systemic lupus erythematosus (SLE), SLE and Sjögren's syndrome (SS), and primary SS. *J Rheumatol* 1998; 25: 63-8.
11. STROMBECK B, EKDAHL C, MANTHORPE R, WIKSTROM I, JACOBSSON L: Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. *Scand J Rheumatol* 2000; 29: 20-8.
12. MCHORNEY CA, WARE JE, JR, RACZEK AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31: 247-63.
13. SARAUX A, DEVAUCHELLE V, JOUSSE S, YOUINOU P: Rituximab in rheumatic diseases. *Joint Bone Spine* 2007; 74: 4-6.
14. EDWARDS JC, SZCZEPANSKI L, SZECHINSKI J *et al*.: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572-81.
15. PERS JO, DEVAUCHELLE V, DARIDON C *et al*.: BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. *Arthritis Rheum* 2007; 56: 1464-77.
16. PIJPE J, VAN IMHOFF GW, SPIJKERVET FK *et al*.: Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. *Arthritis Rheum* 2005; 52: 2740-50.
17. DEVAUCHELLE-PENSEC V, PENNEC Y, MORVAN J *et al*.: Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). *Arthritis Rheum* 2007; 57: 310-7.
18. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
19. PERNEGER TV, LEPLEGE A, ETTER JF, ROUGEMONT A: Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. *J Clin Epidemiol* 1995; 48: 1051-60.
20. LEPLEGE A, ECOSSE E, VERDIER A, PERNEGER TV: The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. *J Clin Epidemiol* 1998; 51: 1013-23.
21. WARE JE, JR, GANDEK B: Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment. *J Clin Epidemiol* 1998; 51: 945-52.
22. WRIGHT JC, MEGER GE: A review of the Schirmer test for tear production. *Arch Ophthalmol* 1962; 67: 564-5.
23. VAN BIJSTERVELD OP: Standardization of the lysozyme test for a commercially available

medium. Its use for the diagnosis of the sicca syndrome. *Arch Ophthalmol* 1974; 91: 432-4.

24. CHISHOLM DM, MASON DK: Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* 1968; 21: 656-60.
25. RUTA DA, HURST NP, KIND P, HUNTER M, STUBBINGS A: Measuring health status in British patients with rheumatoid arthritis: reliability, validity and responsiveness of the short form 36-item health survey (SF-36). *Br J Rheumatol* 1998; 37: 425-36.
26. LEPLEGE A, RUDE N: The importance of patients' own view about their quality of life. *Aids* 1995; 9: 1108-10.
27. Etude santé et soins médicaux. Institut national de la statistique et des études économiques INSEE 2002-03.
28. SEROR R, RAVAUD P, BOWMAN SJ *et al*.: EULAR Sjögren's Task Force. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9. Epub 2009 Jun 28.
29. KVIEN TK, KAASA S, SMEDSTAD LM: Performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. II. A comparison of the SF-36 with disease-specific measures. *J Clin Epidemiol* 1998; 51: 1077-86.
30. HUSTED JA, GLADMAN DD, FAREWELL VT, COOK RJ: Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001; 45: 151-8.
31. BARENDREGT PJ, VISSER MR, SMETS EM *et al*.: Fatigue in primary Sjögren's syndrome. *Ann Rheum Dis* 1998; 57: 291-5.
32. BOWMAN SJ, PILLEMER S, JONSSON R *et al*.: Revisiting Sjögren's syndrome in the new millennium: perspectives on assessment and outcome measures. Report of a workshop held on 23 March 2000 at Oxford, UK. *Rheumatology* (Oxford) 2001; 40: 1180-8.
33. DASS S, BOWMAN SJ, VITAL EM *et al*.: Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. *Ann Rheum Dis* 2008; 67: 1541-4. Epub 2008 Feb 14.