EXTENDED REPORT

Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome

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Objective: To investigate the safety and efficacy of rituximab (RTX) for systemic symptoms in patients with primary Sjögren's syndrome (pSS), and changes in B cell biomarkers.
Patients and methods: The records of 16 patients with pSS according to the American European consensus group criteria were reviewed retrospectively.
Results: Patients, all women, had a median age of 58.5 (range 41–71) years and a disease duration of 9.5 (range 0–25) years. RTX was prescribed for lymphoma (n = 5), refractory pulmonary disease with polysynovitis (n = 2), severe polysynovitis (n = 2), mixed cryoglobulinaemia (n = 5), thrombocytopenia (n = 1) and mononeuritis multiplex (n = 1). The median follow-up duration was 14.5 (range 2–48) months. Three patients experienced adverse events, including one mild serum sickness-like reaction with the presence of human antichimeric antibodies. Efficacy of treatment was observed in 4 of 5 patients with lymphomas and in 9 of 11 patients with systemic involvement. Dryness was improved in only a minority of patients. Corticosteroid dose was reduced in 11 patients. RTX induced decreased rheumatoid factor, γ-globulin and β2-microglobulin levels, and the level of B cell activating factor of the tumour necrosis factor family (BAFF) increased concomitantly with B cell depletion. Five patients were re-treated, with good efficacy and tolerance, except for one with probable serum sickness-like reaction.
Conclusion: This study shows good efficacy and fair tolerance of RTX for systemic features. In addition, RTX allows for a marked reduction in corticosteroid use. Except for BAFF, the level of which increases, serum B cell biomarker levels decrease after taking RTX. Controlled trials should be performed to confirm the efficacy of RTX in pSS.

Primary Sjögren's syndrome (pSS) is characterised by lymphocytic infiltration of exocrine glands, resulting in functional impairment of salivary and lachrymal glands. Clinical features include glandular manifestations, such as dry eyes and dry mouth and systemic manifestations.

Recent studies have focused on the role of B cells in the pathogenesis of pSS.[1 2] B cell activation might result from a marked increase in the level of B cell activating factor of the tumour necrosis factor family (BAFF) in the serum and the target organs of the disease.[3 4] B cells infiltrate the glandular epithelium of salivary ducts and contribute to local production of autoantibodies.[5] Continuous B cell activation probably also leads to the development of lymphomas in pSS, with a 16–18-fold increase, as shown in recent studies.[6 7] Thus, targeting of B cells might be a promising treatment in pSS. As very few data are currently available on the effect of rituximab (RTX) on systemic symptoms of pSS, we retrospectively assessed the tolerance and efficacy of RTX in patients with systemic features of pSS.

PATIENTS AND METHODS

Patient selection

From six French reference centres for pSS, we retrospectively obtained the records of patients who had been treated with RTX, and who had pSS according to the European–American consensus group criteria,[8] and either lymphoma or severe systemic complications. Informed consent was obtained from each patient for the use of RTX, which was given with the agreement of local ethics committees. Four patients have already been reported in a previous study (patients 3, 5, 8 and 12).[9]

Biological assessment

Changes in biological features such as erythrocyte sedimentation rate, C reactive protein concentration, cryoglobulinaemia and B cell biomarkers were recorded. Serum BAFF levels could be retrospectively assessed using ELISA (R&D Systems, Minneapolis, Minnesota) in frozen serum samples of some patients.

Determination of RTX-specific human antichimeric antibodies

Circulating RTX was measured as follows: each serum sample was incubated with a CD20 cell line. After washing the sample, RTX bound to membrane CD20 was detected using fluorescein isothiocyanate (FITC)-labelled anti-human IgG1.[10]

If RTX was not detected, the functional determination of human antichimeric antibodies (HACAs) was performed as follows: FITC-labelled RTX was first incubated with serum at 37°C and then with a CD20 cell line. RTX bound to membrane CD20 was measured by flow cytometry. The mean fluorescence intensity in the patient's serum was compared with that in the control serum of a healthy subject never treated with RTX or other biologicals. The detection of HACA was considered

Abbreviations: BAFF, B cell activating factor of the tumour necrosis factor family; FITC, fluorescein isothiocyanate; HACA, human anti-chimeric antibody; pSS, primary Sjögren's syndrome; RTX, rituximab

positive when the mean fluorescence intensity of the assessed serum was at least 20% less than that of the control serum.

Statistical analysis

All data are presented as medians and ranges. The statistical significance of change in laboratory results after the RTX treatment was measured by Wilcoxon's signed rank test. Values of $p<0.05$ were considered significant.

RESULTS

Patient characteristics

All patients were women. The median age at RTX commencement was 58.5 (41–71) years and median disease duration was 9.5 (0–25) years (table 1).

RTX was prescribed for lymphoma in five patients. Lymphoma was localised in three patients, gastric and *Helicobacter pylori* negative in two (patients 7 and 8), and salivary in one (patient 3), with histological findings of extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue. Patient 4 had stage IV nodal marginal zone B cell lymphoma with peripheral blood leukaemic lymphocytes. Patient 13 showed stage III diffuse large B cell lymphoma.

Two patients showed refractory pulmonary involvement and polysynovitis (patients 2 and 16). In patient 2, RTX was initiated for a 6-month lasting flare of polysynovitis, recent onset of a right pleural effusion and lower lobe condensation, and concomitant renal involvement, related to interstitial polyclonal plasmacytic infiltration, with proteinuria (2 g/day). A 3-month history of polysynovitis and lymphoid interstitial pneumonia led to introduction of RTX in patient 16. Two patients showed severe polysynovitis (patients 1 and 10), including one with marked swelling of the salivary and lachrymal glands and multiple nodules of the face.

RTX was prescribed for symptomatic mixed cryoglobulinaemia in five patients (patients 5, 6, 12, 14 and 15). All five patients showed peripheral neuropathy and purpura, and two also had lower-limb ulcers (patients 5 and 14). Patient 11 received RTX for immune-mediated thrombocytopenia, and patient 9 for mononeuritis multiplex unrelated to cryoglobulinaemia. Thus, no patient was given RTX for glandular symptoms alone.

All patients were given a pulse of methylprednisone (100 mg) and either oral cetirizine (20 mg) or an intravenous pulse of dexchlorpheniramine (5 mg) before each RTX infusion. Four patients received concomitant immunosuppressants.

Tolerance of RTX

Moderate adverse events were observed in three patients. Patient 4 presented with a flu-like syndrome and limited herpetic eruption immediately after the first RTX infusion. Four days after the fourth infusion, patient 1 was readmitted to hospital for fever, arthralgia and purpuric cutaneous lesions. Symptoms resolved after 2 days of oral corticosteroid treatment. Interestingly, the patient was re-treated with RTX 11 months later, without recurrence of the post-infusion reaction. Patient 3 presented with urticaria, arthralgia and fever 3 days after the second infusion. Symptoms recurred after the third and fourth infusions.

Efficacy for lymphoma

In 4 of 5 (80%) patients, complete remission of lymphoma was obtained. In patient 4, peripheral blood leukaemic lymphocytes disappeared and nodal and splenic involvement completely regressed. Normalisation of gastric biopsies was obtained in two patients with gastric lymphoma (patients 7 and 8). Multiple nodal localisations regressed in patient 13, who had large B cell lymphoma. Only one patient with salivary lymphoma was refractory to RTX (patient 3).

Efficacy for systemic features

In 9 of 11 (82%) patients, RTX was efficacious for systemic features; these patients included four with cryoglobulinaemia, two with pulmonary involvement and polysynovitis (one with concomitant renal involvement), two with polysynovitis and one with mononeuritis multiplex. Two patients were refractory to RTX: one with thrombocytopenia and one with cryoglobulinaemia.

Cryoglobulinaemia

Cutaneous vasculitis disappeared in all five patients. Patient 5, with peripheral neuropathy, showed marked improvement of sensitivo-motor deficiency. Peripheral nerve involvement remained stable in three other patients but worsened in one (patient 15), who was considered refractory.

Polysynovitis, pulmonary and renal manifestations

Patient 1 experienced complete remission (no tender or swollen joints), and concomitant glandular swelling also improved considerably. Patient 2 experienced marked improvement of systemic symptoms, with decreased proteinuria (from 2 to 1.1 g/day), complete regression of pleural effusion and pulmonary infiltrates, and improvement of polysynovitis (with a joint count decrease for tenderness and swelling, from 15 to 5 and from 12 to 3, respectively). Patients 10 and 16 had a tender joint count decrease from 20 to 13 and from 17 to 10 and a swollen joint count decrease from 12 to 0 and from 8 to 5, respectively. In patient 16, dyspnoea and cough due to lymphoid interstitial pneumonia disappeared.

Other systemic manifestations

Patient 9, with mononeuritis multiplex unrelated to cryoglobulinaemia, showed lower-limb motor testing improvement, decreased pain and parasthesias, and Romberg's sign regression. In patient 11, with thrombocytopenia, platelet counts remained below 10 000/mm^3 despite RTX treatment.

Efficacy for glandular features

All three patients with major glandular swelling (patients 1, 2 and 6) experienced marked clinical improvement with RTX. Self-reported dryness was improved in 5 (35.7%) patients. Among the 11 patients evaluated, only 2 (18.2%) showed improvement in dryness, shown by disappearance of keratitis assessed by ophthalmological examination. Schirmer evaluation results showed no improvement in seven patients, and worsened in one patient (patient 14). No improvement in salivary flow was observed on salivary glands in eight patients assessed.

Corticosteroid-sparing effects of RTX

Corticosteroid daily dose was lowered in seven and discontinued in four patients who responded to RTX treatment. The median daily dose significantly decreased from 10 to 5 mg/day ($p = 0.003$).

Laboratory features

B cell depletion, monitored in 15 patients, was achieved (peripheral CD19 lymphocyte count <5 cells/μl) in all but one patient (patient 3). Of the patients with sustained remission, B cells reappeared in three patients without relapse, at 9, 16 and 18 months, respectively, after RTX. Median erythrocyte sedimentation rate and C reactive protein concentration decreased, from 60 to 20 mm ($p = 0.009$) and from 11.4 to 4 mg/l ($p = 0.02$), respectively. Cryoglobulinaemia disappeared in four

Table 1 Main characteristics of 16 patients with primary Sjögren's syndrome, treated with rituximab (first treatment)

Patient	Sex/age/disease duration(years)	pSS status: anti-SSA/SSB antibodies/Chisolm–Mason score	Prior Immunosuppressive treatments	Clinical involvement at the beginning of RTX	Number of infusions × dose	Associated immunosuppressor treatments	Adverse event (Y/N)	Efficacy for lymphoma	Efficacy for systemic features	Efficacy for dryness ocular/oral (Y/N)		Follow-up (months)	Prednisone (mg/day) first/last	RF (IU/l) first/last	γ-globulinaemia (g/l) first/last
										Subjective	Objective				
1	F/59/25	SSA SSB/IV	No	Polysynovitis and glandular swelling (cutaneous nodules)	4×375 ms	No	Y(IRR)	NR	Y	N/N	N/N Persitant keratitis Salivary flow=0	15	30/0	1040/415	35.4/26.7
2	F/44/10	SSA SSB/IV	HQ/MTX/Leflu/IFLX/ETA/MMF	Pulmonary, renal involvements and polysynovitis	4×375 ms	No	N	NR	Y	N/N	N/N Stable Schirmer Salivary flow=0	17	30/10	1250/499	87/38
3*	F/43/4	SSA SSB/NA	No	Salivary lymphoma (MALT)	4×375 ms	No	Y(SSR)	N	NR	N/N	NA/NA	14	0/0	499/423	31/26
4	F/71/10	0/III	MTX	Nodal marginal zone lymphoma	4×375 ms	No	Y(IRR)	Y	NR	Y/N	Y/N Regression of keratitis Stable salivary flow	13	0/0	31.5/0	15.8/13.6
5*	F/71/5	SSA/IV	CPH/HQ/AZA	Cryoglobulinaemia	4×375 ms	No	N	NR	Y	N/N	N/N Stable Schirmer Salivary flow=0	27	30/7.5	109/113	8.8/4.6
6	F/53/13	SSA SSB/IV	CPH/AZA	Cryoglobulinaemia	4×375 ms	No	N	NR	Y	N/N	N/N Stable Schirmer Salivary flow=0	21	15/0	55/5	9.2/7
7	F/67/18	SSA/NA	CPH	Gastric, pulmonary lymphoma (MALT)	6×375 ms	Mini-CHOP	N	Y	NR	N/N	NA/NA	48	7.5/7.5	270/0	8.6/7.5
8*	F/58/15	SSA/IV	HQ	Gastric lymphoma (MALT)	4×375 ms	HQ	N	Y	NR	Y/N	Y/NA Regression of keratitis	24	17.5/5	44/0	10.7/6.5
9	F/54/4	SSA SSB/IV	CPH/MMF	Mononeuritis multiplex	4×375 ms	No	N	NR	Y	Y/Y	N/NA Stable Schirmer	13	8/7	139/22	13.4/9.6
10	F/69/12	No/III	HQ/MTX/Leflu/D-peni/IL1RA	Polysynovitis	4×375ms	Leflu	N	NR	Y	N/N	N/NA Stable Schirmer	12	10/7.5	0/0	24.9/14
11	F/63/6	SSA SSB/IV	SZP/goldsalts	Immune mediated thrombocytopenia	4×375 ms	No	N	NR	N	N/N	N/N Stable Schirmer Salivary flow=0	8	5/5	44/22	37.5/26
12*	F/58/2	SSA/NA	CPH	Cryoglobulinaemia	4×375 ms	No	N	NR	Y	NA/NA	NA/NA	25	10/0	170/0	4.8/4.6
13	F/41/9	No/IV	CHP/AZA/MTX/HCQ	Diffuse large B cell lymphoma	4×375 ms	CHOP	N	Y	NR	Y/N	N/N Stable Schirmer Salivary flow=0	15	10/0	NA/0	2.3/4.0
14	F/66/20	No/IV	CPH/AZA/MTX	Cryoglobulinaemia	4×375 ms	No	N	NR	Y	N/N	N/N Worsened Schirmer Salivary flow=0	12	30/10	NA/NA	4.5/5.3
15	F/66/0	SSA/IV	No	Cryoglobulinaemia	4×375 ms	No	N	NR	N	Y/NA	NA/NA	14	0/0	512/NA	NA/NA
16	F/57/3	SSA/II	HQ/MTX	Polysynovitis and pulmonary involvement	2×1 g	No	N	NR	Y	NA/NA	NA/NA	2	30/5	0/0	16.7/15.2

AZA, azathioprine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CPH, cyclophosphamide; D-peni, D penicillamine; ETA, etanercept; F, female; HQ, hydroxy-chloroquine; IFLX, infliximab; IRR, infusion-related reaction; iv, intravenous; Leflu, leflunomide; MALT, mucosa-associated lymphoid tissue; MMF, mycophenolate mofetil; MTX, methotrexate; N, no; NA, not available; NR, not relevant; pSS, primary Sjögren's syndrome; RF, rheumatoid factor; RTX, rituximab; SSA, Sjögren's syndrome antigen; SSB, Sjögren's syndrome B; SSR, serum sickness-like reaction; SZP, salazopyrine; Y, yes.

*Four patients had already been reported in a previous study.[11]

patients assessed. In all patients with anti-SSA/SSB antibodies, the antibodies remained detectable.

The pretreatment and post-treatment B cell biomarker levels were assessed, respectively, just before the first infusion, and 2–4 months after the RTX regimen (fig 1A–D). The median rheumatoid factor (n = 13) level decreased from 124 to 7.5 IU/ml ($p = 0.004$), with complete disappearance in five patients. Median γ-globulin (n = 15), IgG (n = 11) and β2-microglobulin (n = 12) levels decreased from 13.4 to 9.6 g/l ($p = 0.003$), from 10.8 to 7.7 g/l ($p = 0.003$) and from 3.3 to 2.3 mg/l ($p = 0.02$), respectively. The BAFF level was monitored before and after RTX treatment in five cases in four patients (including two who were retreated with RTX; fig 2). The median BAFF level increased from 1.14 (range 0.61–2.84) ng/ml, before RTX treatment, to 3.51 (3.02–8.11) ng/ml 3–7 months after RTX treatment.

HACA level, assessed in eight patients, could not be determined in three because of the persistence of RTX in serum 2–4 months after treatment. Only one patient (patient 3) showed a significant level of HACA. This patient, who developed a serum sickness reaction, was the only patient without B cell depletion after RTX treatment and in whom lymphoma did not respond to treatment.

Follow-up and re-treatment

The median follow-up duration was 14.5 (2–48) months. Five patients relapsed, four experienced a flare of their autoimmune disease, with a median delay of 8 (8–12) months, and lymphoma recurred in one patient initially treated for cryoglobulinaemia (table 2). Clinical relapse was observed 0–3 months after the reappearance of peripheral blood B cells, and was associated with re-increase of B cell biomarkers in all the five patients (fig 1). All were re-treated with RTX. Good efficacy was observed in four of the five patients re-treated for relapse. Patient 10 developed arthralgia, purpura and fever the day after first infusion: all symptoms resolved within a week. Because of this delayed infusion reaction, she was not given a planned second infusion, and no efficacy for polysynovitis was observed. Interestingly, as observed after the first regimen, patients 1 and 2 experienced increased serum BAFF levels, from 0.615 to 3.55 and from 2.87 to 8.11 ng/ml, respectively (fig 2A).

DISCUSSION

The aim of this study was to evaluate the safety and efficacy of RTX in systemic symptoms of pSS. To our knowledge, no published study has focused on the effect of RTX on systemic features of pSS. RTX has been evaluated for pSS-associated lymphoma and in 15 patients with early disease in a recent phase-II trial, in which only one patient showed systemic involvement (table 3).[9 11–20] As there is little published experience regarding RTX in pSS, the tolerability of this treatment and the clinical benefit obtained are noteworthy, despite the retrospective design of the study.

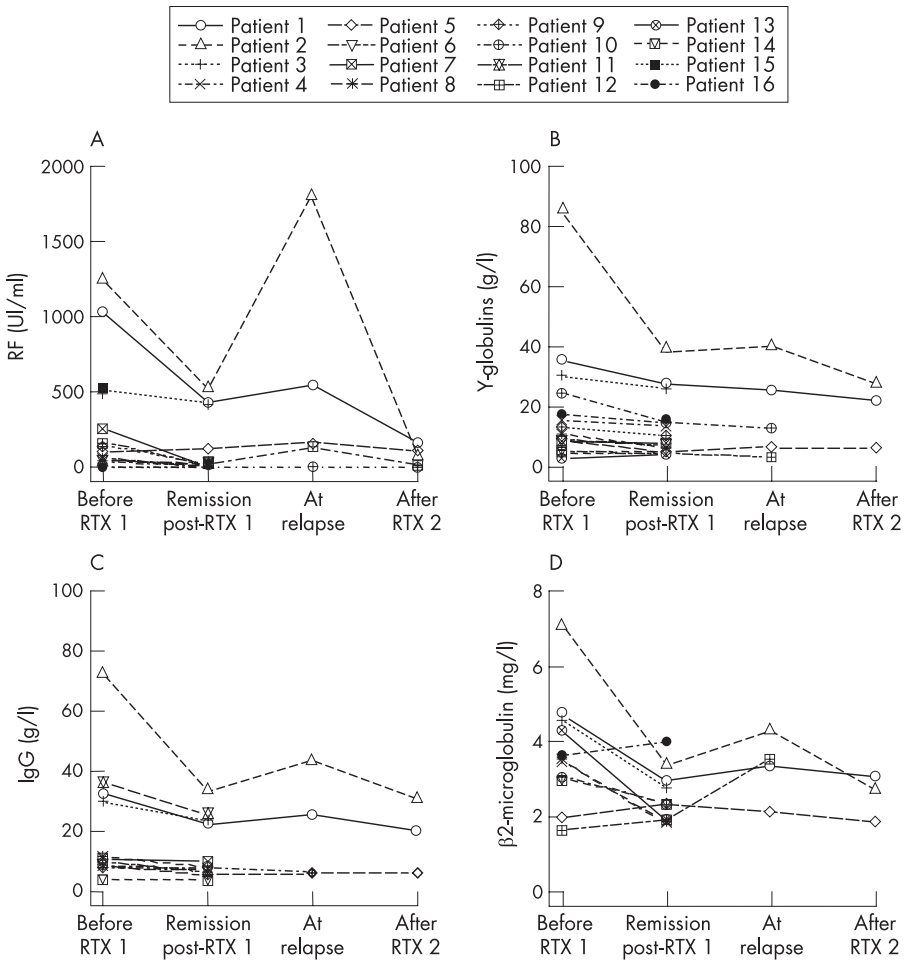

Figure 1 Change in B cell activation biomarkers after first RTX treatment relapse and retreatment with rituximab. (A) Rheumatoid factor, (B) γ-globulins, (C) IgG, (D) β2-microglobulin. Levels were assessed: before first infusion of RTX, 2–4 months after first treatment with RTX, at the time of relapse and at 3 months after the second treatment with RTX.

Table 2 Clinical and biological features of five patients re-treated with rituximab for relapse of symptoms

Patient (cycle of RTX)	Indication of first treatment	Delay of relapse (months)	Reappearance of B cell	Indication of retreatment	Dosage	Adverse event 1st treatment/ retreatment	Efficacy for systemic symptoms or lymphoma/B cell depletion	RF (UI/ml) before/after	γ-globulin (g/l) before/after	IgG (g/l) before/after	β 2-micro-globulin (mg/l) before/after	Prednisone (mg/day) before/after
1 (2)	Polysynovitis, cutaneous nodules	11	Y	Cutaneous nodules	4×375 mg/ms	Y (IRR)/N	Y/Y	405/146	23.7/22.2	25.6/19.8	3.4/3	10/0
2 (2)	Renal, pulmonary, polysynovitis	8	Y	Polysynovitis	2×500 mg/ms	N/N	Y/Y	1820/65	40.8/31.3	44.3/31	4.4/2.72	10/5
5 (2)	Cryoglobulinaemia	8	Y	Cryoglobulinaemia	1×1 g	N/N	N/Y	107/144	6.6/6.4	6/6.2	2.2/1.8	10/40
5 (3)	Cryoglobulinaemia	20	NA	Cryoglobulinaemia	2×1 g	N/N	Y/Y	299/24.3	5.1/4	6/5.1	NA/2.4	30/10
10 (2)	Polysynovitis	12	Y	Polysynovitis	1×375 mg/ms	N/Y (SSR)	N/NA	0/0	12.6/NA	6.1/NA	NA/NA	10/NA
12 (2)	Cryoglobulinaemia	22	Y	Lymphoma	4×375 mg/ms	N/N	Y/Y	139/0	3/NA	NA/NA	3.6/NA	0/0

IgG, immunoglobulin G; IRR, infusion-related reaction; N, no; NA, not available; RF, rheumatoid factor; RTX, rituximab; SSR, serum sickness-like reaction; Y, yes.

This study confirms the efficacy of RTX for lymphoma alone or with a cyclophosphamide, doxorubicin, vincristine, and a prednisone regimen, and shows its efficacy for other systemic features of pSS (82%). In accordance with the results obtained for rheumatoid arthritis,[21] RTX induced clinical improvement in all patients with refractory polysynovitis. RTX was effective for pSS in patients with purpura and ulcerations associated with mixed cryoglobulinaemia, as shown for hepatitis C-associated mixed cryogobulinaemia.[22 23] RTX also had some efficacy in the patient with pSS-related peripheral nerve involvement without cryoglobulinaemia. Finally, it allowed for sustained remission of renal and pulmonary involvement in patients 1 and 2, respectively.

In our study, RTX was effective in reducing the use of corticosteroids in patients with pSS, as shown in other autoimmune diseases.[9 22]

The efficacy of RTX for sicca symptoms was rather limited. Interestingly, in a recent study, no improvement in objective parameters was reported in patients with low residual salivary flow and long disease duration, and conversely, in patients with early pSS, a high rate (64.3%) of objective improvement was observed. If dryness results from glandular damage rather than disease activity, RTX given in later stages of the disease, as in our patients, might be insufficient to restore glandular function.

Immediate infusion-related reactions were observed in only one patient. Such reactions are well described and occur in approximately 30% of patients with rheumatoid arthritis during the first infusion of RTX and in 10% after the remaining infusions.[21 24 25] Serum sickness reaction is a rare complication and has been described in only 14 other cases of patients with

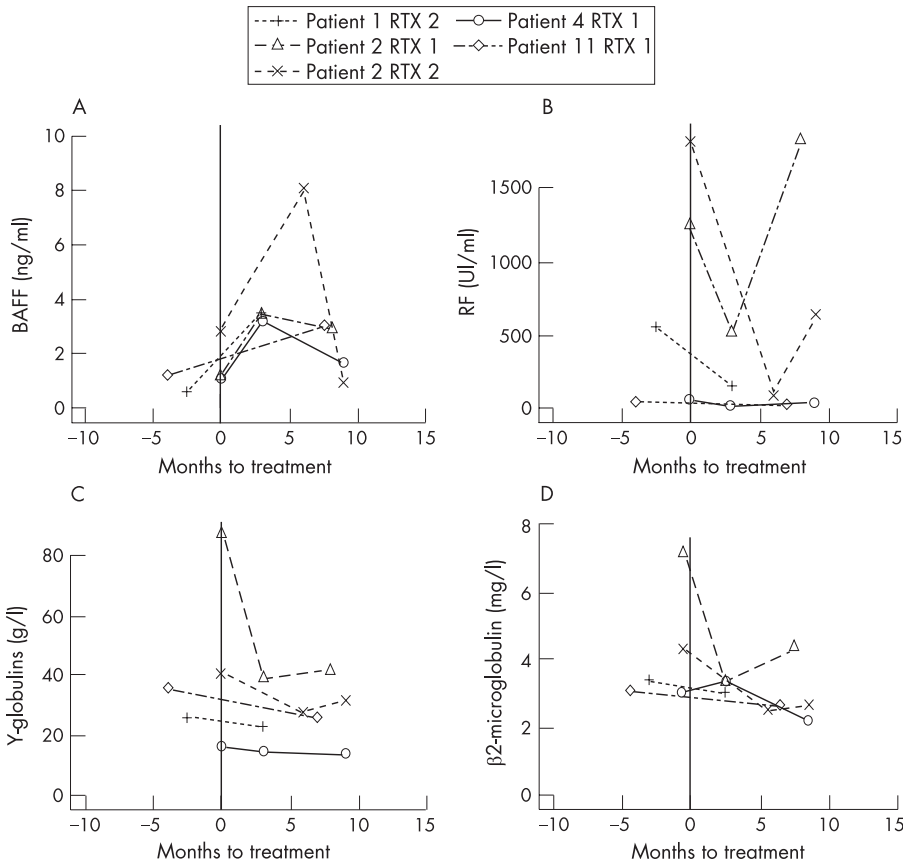

Figure 2 Changes in levels of B cell activating factor of the tumour necrosis factor family (BAFF) and B cell biomarkers, after B cell depletion, in five cases in four patients (including two who were re-treated with rituximab (RTX)). (A) BAFF; (B) Rheumatoid factor (RF); (C) γ-globulins; (D) Beta2-microglobulin. Treatment with RTX was followed by increased serum BAFF level and decreased level of biomarkers of B cell activation. The decrease in BAFF level 8–9 months after B cell depletion was associated with reincrease of B cell biomarker levels.

Table 3 Efficacy and indications of rituximab reported in our and previously published studies

Authors, years	Number of patients	Indications for RTX	Efficacy for lymphoma	Efficacy for systemic features	Efficacy for objective dryness	Efficacy for subjective dryness	Adverse events
Somer, 2003 [13]	1	Lymphoma	Yes	NR	Yes	Yes	No
Voulgarelis, 2004 [14]	4	Lymphoma (4/4)	4/4 (100%)	3/3 (100%)	NM	NM	2/4 (50%) 2 IRR
Harner, 2004 [15]	1	Lymphoma	Yes	NR	NM	Yes	NM
Ramos-Casals, 2004 [16]	2	Lymphoma (2/2)	Yes	NR	NM	NM	NM
Pijpe, 2005 [17]	1	Lymphoma	Yes	NR	Yes	Yes	No
Gottenberg, 2005* [9]	6	Lymphoma (2/6)	1/2 (50%)	NR	N (0/2)	3/6 (50%)	2/6 (33%)
		Systemic features (4/6)	NR	4/4 (100%)			1 SSR, 1IRR
Ahmadi-Simab, 2005 [11]	1	Scleritis	NR	Yes	NM	NM	NM
Pijpe, 2005[18]	15	Lymphoma (7/15)	3/7 (43%)		28.6% (2/7)	Yes	6/14 (43%)
		Early pSS (8/15)		NM	100% (7/7)		3 SSR, 2 IRR
Ring, 2005 [19]	1	Renal tubular acidosis	NR	No	Yes	Yes	No
Voulgarelis, 2006 [20]	6	Lymphoma (6/6)	6/6 (100%)	3/6 (50%)	NM	No	2/6 (33%)
Present study*	16	Lymphoma (5/16)	4/5 (80%)	NR	2/16 (18%)	5/16 (36%)	4/16 (25%)
		Systemic features (11/16)	NR	9/11 (82%)			2 SSR, 2 IRR

IRR, infusion-related reaction; NM, not mentioned; NR, not relevant; pSS, primary Sjögren's syndrome; RTX, rituximab; SSR, serum sickness-like reaction.
*Four patients are common between the two studies.

autoimmune diseases.[18 26–30] Regarding the heterogeneous presentation of this complication in the literature, some cases of supposed serum sickness reaction could be merely delayed RTX infusion-related reactions rather than ''authentic'' serum sickness diseases. Among our three patients who experienced delayed infusion-related reactions, one patient did not present with a serum sickness reaction: patient 1, who was re-treated with no recurrence of delayed RTX infusion-related reaction. Moreover, she did not develop HACAs. Conversely, the development of HACAs supports the diagnosis of a true serum sickness reaction in patient 3, and might also have impaired B cell depletion and efficacy of RTX in this patient.

For most of our patients, the level of biomarkers of B cell activation, such as rheumatoid factor, β2-microglobulin, IgG and γ-globulin, decreased after RTX treatment and increased before clinical relapse (fig 1). The increase in serum BAFF level after RTX treatment was an unanticipated and interesting result. Identical findings have been described recently in patients with rheumatoid arthritis treated with RTX.[31] The increase in BAFF level might be the result of depletion of B cells, which are the major source of BAFF receptors, leading to the inability of BAFF to target its receptors. BAFF increase may also represent a feedback mechanism to maximise the proliferation and survival of B cells back to normal levels. A prospective study of additional patients is now required to investigate these hypotheses.

In conclusion, the present study shows the efficacy of RTX for systemic features and glandular swelling in pSS. In addition, RTX allowed for a marked reduction in corticosteroid use. These results illustrate the potential interest of RTX treatment for a disease, often refractory to other immunosuppressive agents. Further controlled trials are now required to confirm the efficacy of RTX in pSS.

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